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***CLAIMS/US PATENTS (File 340, 341, 942)
***Kompa Middle Eat/Africa/Mediterranean (File 585)
***Kompa Aia/Pacific (File 592)
***Kompa Central/Eatern Erope (File 593)
***Kompa Canada (File 594)

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File   1:ERIC  1966-2001/No 02
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      18nov01 08:59:59 User208760 Session D1981.1
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       (c) 2001 The Dialog Corporation

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  File   5:Biosis Previews(R)  1969-2001/Nov W2
         (c) 2001 BIOSIS
  File  73:EMBASE  1974-2001/Nov W2
         (c) 2001 Elsevier Science B.V.
*File  73: For information about Explode feature please
see Help News73.
  File 155:MEDLINE(R)  1966-2001/Dec W2
  File 399:CA SEARCH(R)  1967-2001/UD=13521
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           13904  CLL
            7345  CD20
           13067  CD40
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 2/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

13107668   BIOSIS NO.: 200100314817
Enhancement of antibody dependent cellular cytotoxicity (ADCC) against
  malignant B cells by trimeric CD40L.
AUTHOR: Jia Li(a); Epstein Alan(a); Douer Dan(a); Mohrbacher Ann(a)
AUTHOR ADDRESS: (a)University of Southern California, Los Angeles, CA**USA
JOURNAL: Blood  96 (11 Part 2):p288b-289b November 16, 2000
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of
Hematology  San Francisco, California, USA  December 01-05, 2000
SPONSOR: American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: CD40 expressed on B cells triggered by CD40 ligand
  (CD40L) on T cells promotes B cell activation and proliferation. Such
  CD40L activation can also predispose B cells to apoptosis by activation
  induced cell death (AICD). Lym-1 and chCLL-1 are humanized monoclonal
  antibodies directed against B cell restricted HLA-DR epitopes, which may
  be upregulated during activation of B cells. To see if CD40L activation
  could enhance antibody targeting or ADCC against malignant B cells,
  peripheral blood lymphocytes (PBL) from 14 CLL patients were
  incubated in standard media with CD40L 400ng/ml for 48 hours at 370C.
  Expression of B cell lineage markers (CD19) was examined by dual color
  flow cytometry confirming 70-95% purity of CLL cells. Enhancement
  of ADCC killing of B cells by Lym-1 and chCLL-1, vs antiCD20 Ab or TNT
  (irrevalent control chimeric Ab), after incubation of B cell targets with
  CD40L was assessed by standard chromium release assays at 48 hours.
  Upregulation of antibody target binding after 48 hours incubation with
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media or CD40L was assessed by comparative fluorescence intensity on flow cytometry. CD40L strongly enhanced antibody dependent cellular cytotoxicity against malignant B cells. Preincubation with CD40L showed synergistic killing only with B cell specific chimeric Abs; killing in media control or with an irrelevant antibody was not enhanced. This enhancement of ADCC with Lym1, chCLL1, and anti **CD20** Abs showed strong statistical significance by two tailed t-Test. Activation by CD40L also significantly upregulated target binding two-fold by these HLA-DR related antibodies used here, but did not upregulate **CD20**, a common B cell antigen. This fits the model that these antibodies target part of the B cell activation complex. There was no correlation (R2 <0.5) between absolute target antigen upregulation and enhanced ADCC in individual samples. Given this, vulnerability to antibody directed cytotoxicity may reflect B cell activation status triggered by CD40L. As these Abs and CD40L have been developed for clinical use, these findings may provide new strategies for immunotherapy combinations to overcome resistance to therapeutic Abs.

2/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12942293 BIOSIS NO.: 200100149442
CpG DNA increases primary malignant B cell expression of costimulatory molecules and target antigens.
AUTHOR: Jahrsdorfer Bernd; Hartmann Gunther; Racila Emil; Jackson Wallen; Muhlenhoff Lars; Meinhardt Gerold; Endres Stefan; Link Brian K; Krieg Arthur M; Weiner George J(a)
AUTHOR ADDRESS: (a)University of Iowa Cancer Center, University of Iowa, 5970Z JPP, Iowa City, IA, 52242: george-weiner@uiowa.edu**USA
JOURNAL: Journal of Leukocyte Biology 69 (1):p81-88 January, 2001
MEDIUM: print
ISSN: 0741-5400
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Multiple factors, including expression of costimulatory molecules, antigen-presenting molecules, and target antigens, likely impact the efficacy of antibody therapy and other approaches to the immunotherapy of B cell malignancy. Unmethylated CpG-dinucleotides in select base contexts ("CpG motifs") that resemble sequences found in bacterial DNA are potent immunostimulatory agents capable of inducing a complex immune response, including a strong B cell stimulus. We examined the effect of a potent human CpG oligonucleotide (CpG ODN 2006) on different types of primary human malignant B cells and reactive follicular hyperplasia. CpG oligodeoxynucleotide (CpG ODN), but not control (non-CpG ODN), increased the expression of costimulatory molecules (**CD40**, CD80, CD86, CD54) on malignant B cells without altering the phenotype of B cells obtained from reactive follicular hyperplasia. CpG ODN also enhanced expression of class I and class II MHC in most samples. **CD20** expression was increased in response to CpG ODN, most notably in B-**CLL** and marginal zone lymphoma. An inverse correlation was found between baseline expression of **CD20** and **CD40** and their expression after exposure to CpG ODN, thus the most significant increase in expression of these molecules was found in those samples that had the lowest baseline levels. In conclusion, CpG ODN can lead to increasing expression of molecules involved in costimulation, antigen presentation, and as targets for antibody-based therapy and deserve further evaluation as potential immunotherapeutic agents for B cell malignancy.

2/7/3 (Item 3 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

11447606 BIOSIS NO.: 199800228938
Chronic lymphocytic leukemia B cells can express **CD40** ligand and demonstrate T-cell type costimulatory capacity.
AUTHOR: Schattner Elaine J(a); Mascarenhas John; Reyfman Inna; Koshy Mary; Woo Caroline; Friedman Steven M; Crow Mary K
AUTHOR ADDRESS: (a)Room C-640, Cornell Univ. Med. Coll., 1300 York Ave., New York, NY 10021**USA
JOURNAL: Blood 91 (8):p2689-2697 April 15, 1998
ISSN: 0006-4971
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Chronic lymphocytic leukemia (**CLL**) is characterized by a clonal expansion of CD5!+ B cells in the peripheral blood. Associated immune aberrations include abnormal Th-cell function and pathogenic autoantibodies. Under most circumstances, **CLL** B cells do not proliforate in culture and express a limited repertoire of surface antigens, including CD19, **CD20**, CD23, CD27, **CD40**, and CD70. In this report, we demonstrate that freshly isolated B cells from a subset of **CLL** cases constitutively express **CD40** ligand (CD40L, CD154), a member of the tumor necrosis factor family which is normally expressed by activated CD4!+ T cells and mediates T-cell-dependent B-cell proliferation and antibody production. The degree of CD40L expression varied considerably among the **CLL** cases examined. CD40L was detected in purified **CLL** B cells by immunofluorescence flow cytometry, by RT-PCR, and by immunoprecipitation. To demonstrate that CD40L in the **CLL** B cells is functional, we used irradiated **CLL** cells to stimulate IgG production by target, nonmalignant 8 cells in coculture. The **CLL** B cells induced IgG production by normal B cells to a similar degree as did purified T cells in a process which was partially inhibited by monoclonal antibody to CD40L. This is one of the first reports of CD40L expression in a B-cell tumor. The data suggest that CD40L in the tumor cells may be a factor in the generation of pathologic antibodies by normal B cells in some patients with **CLL**.

2/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10095218 BIOSIS NO.: 199598550136
Antibodies are capable of directing superantigen-mediated T cell killing of chronic B lymphocytic leukemia cells.
AUTHOR: Gidlof C; Dohlsten M; Kalland T; Totterman T H(a)
AUTHOR ADDRESS: (a)Dep. Clinical Immunol., Univ. Hosp., S-751 85 Uppsala** Sweden
JOURNAL: Leukemia (Basingstoke) 9 (9):p1534-1542 1995
ISSN: 0887-6924
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The bacterial superantigen staphylococcal enterotoxin A (SEA) is a highly potent activator of cytotoxic T cells when presented on MHC class II molecules of target cells. Our earlier studies showed that such SEA-directed T cells efficiently killed chronic B lymphocytic leukemia (B-**CLL**) cells. With the ultimate goal to replace the natural specificity of SEA for MHC class II molecules with the specificity of a monoclonal antibody (mAb), we initially made a mutated protein A-SEA (PA-SEAm) fusion protein with gt 100-fold reduced binding affinity for MHC class II compared to native SEA. The fusion protein was successfully

used to direct T cells to B-**CLL** cells coated with different B lineage specific (CD19, **CD20**) or associated (CD37, **CD40**) mAbs. The PA-SEAm protein was 10-100-fold more potent against mAb coated compared to uncoated HLA class II+ B-**CLL** cells. No correlation was seen between the amount of mAb bound to the cell surface and sensitivity to lysis. Preactivation of B-**CLL** cells by phorbol ester increased their sensitivity, and lysis was dependent on ICAM-1 molecules. However, no preactivation of the target cells was needed when a cocktail of two or four mAbs was used. Circulating leukemia and spleen cells were equally well killed. We conclude that the natural target specificity of SEA, MHC class II, can be reduced by mutagenesis and novel binding specificity can be introduced by linkage to tumor reactive mAbs. Our findings encourage the construction of recombinant SEA mutant fusion proteins for specific T cell therapy of hematopoietic tumors such as B-**CLL**.

2/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09615532 BIOSIS NO.: 199598070450
In vitro culturing of leukemic B cells from **CLL** patients using feeder cells and **CD40** ligand.
AUTHOR: Buske C(a); Gogowski G; Feuring-Buske M; Koenemann S; Widmer M; Banchereau J; Lebien T W; Schreiber K; Hiddemann W; Woermann B
AUTHOR ADDRESS: (a)Dep. Intern. Med., Univ. Goettingen, Goettingen**Germany
JOURNAL: Blood 84 (10 SUPPL. 1):p454A 1994
CONFERENCE/MEETING: Abstracts Submitted to the 36th Annual Meeting of the American Society of Hematology Nashville, Tennessee, USA December 2-6, 1994
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

2/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07614014 BIOSIS NO.: 000091131898
DETECTION OF ACTIVATION ANTIGENS ON CHRONIC LYMPHOCYTIC LEUKEMIA CELLS
AUTHOR: PALOCZI K; POCSIK E; MIHALIK R; BENCZUR M; DEMETER J; SOLTI V; PETRANYI G; HOLLAN S R
AUTHOR ADDRESS: NATL. INST. HAEMATOLOGY BLOOD TRANSFUSION, BUDAPEST, P.O. BOX 44, H-1502, HUNGARY.
JOURNAL: LEUK LYMPHOMA 3 (1). 1990. 31-36. 1990
CODEN: LELYE
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The peripheral blood mononuclear cells of patients with chronic lymphocytic leukaemia were characterized by the presence of a variety of cell surface differentiation antigens. The cells of 20 patients were found to be of B-cell phenotype when studied with antibodies directed against CD19, **CD20**, HLA-DR and sIg. Furthermore, a significant percentage of the cells gave a positive reaction with the monoclonal antibody to CD5. On the other hand, the **CLL**-cells did not express the CD21 antigen (C3d receptor, EBV receptor). We studied in parallel the presence of various activation antigens using 19 monoclonal antibodies grouped into 7 clusters (CD25, CD30, **CD40**, CD69, CD70 CD 39, CD71). A significantly higher percentage of the **CLL** cells expressed activation antigens than lymphocytes from healthy controls. The percentage of CD3/HLA+DR+cells, compared to the healthy control lymphocytes was not increased in the **CLL** patients, and the activated cells in **CLL** were found to have characteristics of B-cells. Based on these results, we suggest that the **CLL** cells,

like the cells in Hodgkin's disease and T-cell lymphoma, are not resting, but activated B-cells or the neoplastic aberrants of activated cells.

2/7/7 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

11266163 EMBASE No: 2001262786
Clonal variation in the B-lineage acute lymphoblastic leukemia response to multiple cytokines and bone marrow stromal cells
Shah N.; Oseth L.; Tran H.; Hirsch B.; LeBien T.W.
T.W. LeBien, Univ. of Minnesota Cancer Center, Mayo Mail Code 806, 420 Delaware Street SE, Minneapolis, MN 55455 United States
AUTHOR EMAIL: lebie001@tc.umn.edu
Cancer Research (CANCER RES.) (United States) 01 JUL 2001, 61/13 (5268-5274)
CODEN: CNREA ISSN: 0008-5472
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 50

The acquisition of genetic abnormalities in human B-lineage acute lymphoblastic leukemia (ALL) culminates in the clonal expansion of bone marrow (BM)-derived leukemic blasts. However, the response of leukemic cells to signals transduced by the BM microenvironment is not completely understood. The present study describes a new human B-lineage ALL cell line designated BLIN-4 (B LINeage-4). BLIN-4 cells respond to multiple cytokines/human BM stromal cell-derived molecules. One subline (BLIN-4E) undergoes cell death in the absence of BM stromal cells or cytokines and slowly proliferates on human BM stromal cells supplemented with interleukin (IL)-7 + FLT3-ligand. Another subline (BLIN-4L) slowly proliferates in the absence of cytokines and BM stromal cells and shows robust proliferation on BM stromal cells supplemented with IL-7 + FLT3-ligand. Although human BM stromal cells are comparable with IL-7 + FLT3-ligand in supporting proliferation of BLIN-4L cells, neutralizing antibody experiments demonstrate that BLIN-4L expansion on BM stromal cells is IL-7/FLT3-ligand independent. BLIN-4L could also respond to human thymic stromal lymphopoietin. BLIN-4E and BLIN-4L have the identical immunoglobulin heavy chain rearrangement and a CD10SUP+/CD19SUP+/CD20SUP-/CD22SUP+/**CD40** SUP+/mu heavy chainSUP- phenotype. The original BM leukemic blasts harbored a ring chromosome 4 with a low percentage of cells also having either trisomy 8 or trisomy 18. The BLIN-4 sublines maintained the ring chromosome 4, but the trisomy 8 and trisomy 18 segregated into BLIN-4E and BLIN-4L, respectively. Thus, the BLIN-4 sublines exhibit biological characteristics consistent with a potential evolution in B-lineage ALL involving subclones with decreasing requirements on the BM microenvironment.

2/7/8 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07299384 EMBASE No: 1998199909
The cellular biology of B-cell chronic lymphocytic leukemia
Jurlander J.
J. Jurlander, Department of Hematology, Finsencenter, Rigshospitalet, 2100 Copenhagen Denmark
Critical Reviews in Oncology/Hematology (CRIT. REV. ONCOL. HEMATOL.) (Ireland) 1998, 27/1 (29-52)
CODEN: CCRHE ISSN: 1040-8428
PUBLISHER ITEM IDENTIFIER: S1040842897100087
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 266

In conclusion, B-**CLL** cells through their immunophenotype have the functional potential required to interact with cells in what has been called the immunological synapse, i.e. the cognate interactions between T-cells, antigen-presenting cells and B-cells during immunopoiesis. The data reviewed herein provides substantial evidence to suggest that B-**CLL** cells in fact can interact, not only with T-cells but also with endothelial cells and stromal cells in the bone marrow. These interactions, in particular signaling through **CD40**, contribute to extended survival and proliferation of B-**CLL** cells and, thereby, the risk of complete malignant transformation of the clone. Therefore, this review would suggest that the answers to how B-**CLL** is initiated may be found in molecules responsible for the normal regulation of immunopoiesis. Transformation to malignancy, by contrast, is likely to be caused by loss of control over the G1 restriction in the cell cycle in B-**CLL** cells.

2/7/9 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

06471372 EMBASE No: 1996126294
CD20 and **CD40** mediated mitogenic responses in B-lineage acute lymphoblastic leukaemia
Smiers F.J.; Van Paassen M.; Hahlen K.; Lowenberg B.; Touw I.P.
Institute of Haematology, Erasmus University, P.O. Box 1738,3000 DR Rotterdam Netherlands
British Journal of Haematology (BR. J. HAEMATOL.) (United Kingdom) 1996, 93/1 (125-130)
CODEN: BJHEA ISSN: 0007-1048
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Activation of **CD20**, a cross-membrane ion channel, induces cell cycle progression from Ginf 0 to Ginf 1 in B lymphocytes. Subsequent activation of **CD40**, a membrane receptor of the nerve growth factor receptor superfamily, transits the B cells to the S phase. **CD40** may also act synergistically in combination with IL-4 (B lymphocytes) or IL-3/IL-7 (B-cell precursors). We investigated the proliferative responses of B-lineage acute lymphoblastic leukaemia (ALL) cells to **CD20**/**CD40** activation. In 18/56 ALL cases, **CD20** activation resulted in significant increases in DNA synthesis. Similar, although more moderate, effects were seen of activation of **CD40** in 10/44 cases. Responses to **CD20** or **CD40** activation were independent of co-stimulation with IL-3, IL-4 or IL-7, and various cocktails of the different growth stimuli did not act synergistically.

2/7/10 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

06265488 EMBASE No: 1995302077
Antibodies are capable of directing superantigen-mediated T cell killing of chronic 8 lymphocytic leukemia cells
Gidlof C.; Dohlsten M.; Kalland T.; Totterman T.H.
Dept of Clinical Immunology, University Hospital,S-751 85 Uppsala Sweden
Leukemia (LEUKEMIA) (United Kingdom) 1995, 9/9 (1534-1542)
CODEN: LEUKE ISSN: 0887-6924
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The bacterial superantigen staphylococcal enterotoxin A (SEA) is a highly potent activator of cytotoxic T cells when presented on MHC class II molecules of target cells. Our earlier studies showed that such SEA-directed T cells efficiently killed chronic B lymphocytic leukemia (B-**CLL**) cells. With the ultimate goal to replace the natural specificity

of SEA for MHC class II molecules with the specificity of a monoclonal antibody (mAb), we initially made a mutated protein A-SEA (PA-SEAm) fusion protein with > 100-fold reduced binding affinity for MHC class II compared to native SEA. The fusion protein was successfully used to direct T cells to B-**CLL** cells coated with different B lineage specific (CD19, **CD20**) or associated (CD37, **CD40**) mAbs. The PA-SEAm protein was 10-100-fold more potent against mAb coated compared to uncoated HLA class IIsup + B-**CLL** cells. No correlation was seen between the amount of mAb bound to the cell surface and sensitivity to lysis. Preactivation of B-**CLL** cells by phorbol ester increased their sensitivity, and lysis was dependent on ICAM-1 molecules. However, no preactivation of the target cells was needed when a cocktail of two or four mAbs was used. Circulating leukemia and spleen cells were equally well killed. We conclude that the natural target specificity of SEA, MHC class II, can be reduced by mutagenesis and novel binding specificity can be introduced by linkage to tumor reactive mAbs. Our findings encourage the construction of recombinant SEA mutant fusion proteins for specific T cell therapy of hematopoietic tumors such as B-**CLL**.

2/7/11 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

05785538 EMBASE No: 1994193129
Monoclonal expansion of immunoglobulin non-secreting CD5+ CD11c+ CD38+ B-cells in a rare case of chronic lymphoplasmacytoid leukaemia
Grande M.; Lucivero G.; Gambatesa V.; Schiraldi O.; Bonomo L.
Via Cavour 24,I-74100 Taranto Italy
Nouvelle Revue Francaise d'Hematologie (NOUV. REV. FR. HEMATOL.) (France) 1994, 36/3 (235-240)
CODEN: NRFHA ISSN: 0029-4810
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH; FRENCH

We present the clinical and immunological features of a rare case of chronic lymphoid leukaemia with lymphoplasmacytoid morphology. The patient was first admitted suffering from weakness, pallor, dyspnoea, marked splenomegaly, hepatomegaly and systemic lymphadenopathy and panhypogammaglobulinaemia. White blood cell count revealed important leukocytosis (220 x 10sup 9 WBC/l) with 2% neutrophils and 98% lymphoid cells showing lymphoplasmacytoid features, while lymphoid cells of identical morphology severely infiltrated the bone marrow and lymph nodes. The disease, initially controlled by non aggressive chemotherapy over a period of 30 months, later evolved to a clinical and haematological picture suggestive of Richter's syndrome. Immunophenotyping of the leukaemic cells demonstrated a monoclonal expansion of B-cells bearing surface markers of typical **CLL** (CD5, CD19, **CD20**, CD21, CD22, CD23, CD24, **CD40** and low density IgM+IgD/kappa) and also the CD11c and CD38 antigens. A proportion of these cells expressed activation markers (CD25, CD69 and CD71). Following in vitro activation with TPA or PWM, the cells responded by weak incorporation of 3H-TdR but failed to secrete immunoglobulins. These findings confirm the broad morphological, phenotypical and clinical spectrum of chronic lymphoid leukaemias.

2/7/12 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

04214563 EMBASE No: 1990097105
Immunobiology of chronic lymphocytic leukemia
Freedman A.S.
Division of Tumor Immunology, Dana-Farber Cancer Institute, 44 Binney Street,Boston, MA 02115 United States
Hematology/Oncology Clinics of North America (HEMATOL. ONCOL. CLIN.

NORTH AM.) (United States) 1990, 4/2 (405-429)
CODEN: HCNAE ISSN: 0889-8588
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The majority of CLLs are of B lineage derivation with about 5 per cent of cases of T lineage. Although morphologically resembling the small peripheral blood B cell, by virtue of the expression of B cell restricted and associated cell surface antigens, B-CLLs are not the neoplastic counterparts of normal resting B cells. Similar to the peripheral blood B cell, B-CLLs express CD19, **CD20**, CD21, CD24, **CD40**, CD44, CD45R, and sIgM/D. However, unlike peripheral blood B cells, B-CLLs generally do not express C3b complement receptor, LFA-1, or CD22. In addition, B-CLLs express the T cell associated antigen CD5, and a number of antigens induced on normal B cells following in vitro activation (B5, Blast-1, CD23). These findings support the hypothesis that B-CLLs are the neoplastic counterparts of one or more unique subpopulations of normal B cells. Normal CD5+ B cells, which phenotypically resemble B-**CLL**, are present in fetal lymphoid tissues and in small numbers in adults. Moreover, normal CD5+ B cells are present in increased numbers in patients with autoimmune diseases and a subset of normal in vitro activated B cells phenotypically resemble B-**CLL**. Similar studies into the state of differentiation of T-**CLL** cells suggest that although most cases resemble normal activated T helper cells, a significant number are the neoplastic counterparts of natural killer cells. Recent studies have examined the function of B and T cells in B-**CLL**. Although controversial, these studies suggest that the in vitro response to mitogens and cytokines of B-**CLL** cells is abnormal. T cell proliferation in B-**CLL** is depressed due to an inability to produce sufficient T cell growth factor (IL-2) as well as poor response to exogenous IL-2 possibly from ineffective IL-2 receptor expression. Purified populations of T helper and T suppressor cells demonstrate insufficient support of Ig production by normal B cells as well as excess suppression, respectively. These studies have further supported the previous hypothesis that the depressed cellular and humoral immunity in **CLL** is multifactorial with both abnormal B and T cell function.

2/7/13 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09837135 98351123 PMID: 9686504
[A case of chronic B cell lymphocytic leukemia with expression of CD8 antigen on leukemic cells]
Przypadek przewleklej bialaczki limfatycznej B komorkowej z ekspresja antygenu CD8 na bialaczkowych komorkach.
Rolinski J; Rupniewska ZM; Wasik-Szczepanek EA
Zakladu Immunologii Klinicznej AM w Lublinie.
Polskie archiwum medycyny wewnetrznej (POLAND) Jan 1998, 99 (1) p48-55, ISSN 0032-3772 Journal Code: PAV
Languages: POLISH
Document type: Journal Article
Record type: Completed
CD8 antigen is present on the surface of cytotoxic-suppressor T cells, NK cells and majority of thymocytes. Expression of CD 8 is associated with CD 3 antigen, which is a part of a T cell receptor. However, CD 8 antigen is undetectable on normal B cells. In sporadic cases of B cell-chronic lymphocytic leukaemia (B-**CLL**) it was found on leukaemic B cells. We report a case of B-**CLL** of benign course with CD19+, CD5+, **CD40** +, CD19+, **CD20** +, CD19+, CD19+HLADR+ leukaemic cells expressing CD8 antigen on CD19+ leukaemic cells. It seems that original neoplasms source was localized out of bone marrow. We suggest that the origin of the target cell for neoplasms transformation could be CD5+ B cell and CD8+ T cell gamma + delta + CD8+.
Record Date Created: 19980901

2/7/14 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08286693 95061374 PMID: 7971244
Monoclonal expansion of immunoglobulin not-secreting CD5+ CD11c+ CD38+ B-cells in a rare case of chronic lymphoplasmacytoid leukaemia.
Grande M; Lucivero G; Gambatesa V; Schiraldi O; Bonomo L
Second Institute of Medical Clinics, University of Bari, Medical School, Italy.
Nouvelle revue francaise d'hematologie (GERMANY) Jun 1994, 36 (3) p235-40, Journal Code: O6S
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We present the clinical and immunological features of a rare case of chronic lymphoid leukaemia with lymphoplasmacytoid morphology. The patient was first admitted suffering from weakness, pallor, dyspnoea, marked splenomegaly, hepatomegaly and systemic lymphadenopathy and panhypogammaglobulinaemia. White blood cell count revealed important leukocytosis (220 x 10(9) WBC/l) with 2% neutrophils and 98% lymphoid cells showing lymphoplasmacytoid features, while lymphoid cells of identical morphology severely infiltrated the bone marrow and lymph nodes. The disease, initially controlled by non aggressive chemotherapy over a period of 30 months, later evolved to a clinical and haematological picture suggestive of Richter's syndrome. Immunophenotyping of the leukaemic cells demonstrated a monoclonal expansion of B-cells bearing surface markers of typical **CLL** (CD5, CD19, **CD20**, CD21, CD22, CD23, CD24, **CD40** and low density IgM+IgD/kappa) and also the CD11c and CD38 antigens. A proportion of these cells expressed activation markers (CD25, CD69 and CD71). Following in vitro activation with TPA or PWM, the cells responded by weak incorporation of 3H-TdR but failed to secrete immunoglobulins. These findings confirm the broad morphological, phenotypical and clinical spectrum of chronic lymphoid leukaemias.
Record Date Created: 19941129

2/7/15 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05931365 89007205 PMID: 2459071
Triggering of neoplastic B cells via surface IgM and the cell surface antigens **CD20** and CDw40. Responses differ from normal blood B cells and are restricted to certain morphologic subsets.
Beiske K; Clark EA; Holte H; Ledbetter JA; Smeland EB; Godal T
Department of Pathology, Norwegian Radium Hospital, Oslo.
International journal of cancer. Journal international du cancer (UNITED STATES) Oct 15 1988, 42 (4) p521-8, ISSN 0020-7136 Journal Code: GQU
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
By raising monoclonal antibodies (MAbs) against B cells, a number of cell surface molecules have recently been identified which after binding by their specific antibody can trigger B cells, either alone or in co-operation with antibodies to surface immunoglobulin (sIg). The anti-**CD20** (Bp35) MAb IF5 can deliver a strong activation signal to resting normal B cells, and the anti-CDw40 (Bp50) MAb G28-5 can promote activated G1 B cells to enter S phase. These antibodies were tested for their functional effects in vitro on suspended cells from 17 follicle-center-cell (FCC) lymphomas, 5 cases of chronic lymphatic **B-cell leukemia** (B-**CLL**) and 8 cases of various histological types. Changes in cellular volume, RNA and DNA synthesis were compared with the results obtained with a polyclonal anti-mu [F(ab')2] antiserum, a MAb to surface IgM (AF6), 12-O-tetradecanoyl-phorbol-13-acetate (TPA) and B-cell growth factor (low-molecular-weight BCGF). Our data reveal differences in the requirements for triggering of various B-cell subsets: cells from

CLL responded strongly to TPA but not to anti-mu, which is a potent stimulator not only of normal B cells but also of cells from individual cases of FCC lymphomas. Our observations suggest that the differentiation stage of B-**CLL** cells is distinct from that of small resting B cells from peripheral blood. Centrocytic lymphomas could not be activated by any of the reagents. **CD20**-mediated triggering was seen in neoplastic B cells from only 4 of 30 cases, indicating that most B-cell neoplasias were not responsive to this activation pathway. In contrast, the anti-CDw40 MAb consistently stimulated DNA synthesis together with anti-mu or TPA in cells from FCC lymphomas, but not from **CLL**. Together, these results suggest that activation in different neoplastic B-cell subsets depends on distinct signal transduction mechanisms.
Record Date Created: 19881121

2/7/16 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

134365708 CA: 134(26)365708x PATENT
Treatment of B cell malignancies using anti-CD40L antibodies in combination with anti-CD20 antibodies and/or chemotherapeutics and radiotherapy
INVENTOR(AUTHOR): Hanna, Nabil; Hariharan, Kandasamy
LOCATION: USA
ASSIGNEE: Idec Pharmaceuticals Corporation
PATENT: PCT International ; WO 0134194 A1 DATE: 20010517
APPLICATION: WO 2000US30426 (20001106) *US 435992 (19991108)

5/7/39 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE

06313864 EMBASE No: 1995335544
Study of **CD40 ligand** expression in B-cell chronic lymphocytic **leukemia**
Brugnoni D.; Rossi G.; Tucci A.; Cattaneo R.; Airo P.
Servizio di Immunologia Clinic, Spedali Civili, piazzale Spedali Civili 1,25123 Brescia Italy
Haematologica (HAEMATOLOGICA) (Italy) 1995, 80/5 (440-442)
CODEN: HAEMA ISSN: 0390-6078
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

CD40 ligand (**CD40L**) is a membrane molecule that plays a key role in T cell-B cell cooperation, providing B cells the helper signals needed for activation, proliferation, differentiation and prevention of apoptosis. Patients with B-cell chronic lymphocytic **leukemia** (B-CLL) were studied to verify the following hypotheses: a) whether defective **CD40L** expression on activated T cells could account for deficient helper signals and therefore for hypogammaglobulinemia; b) whether aberrant **CD40L** expression on B cells could be a mechanism by which leukemic cells stimulate themselves via CD40 to escape apoptosis. Results showed physiological expression of **CD40L** on in vitro activated CD4sup + cells, while this expression was absent on fresh and activated B cells. Abnormalities in CD40/**CD40L** interaction do not seem to play a role either in the pathogenesis of hypogammaglobulinemia or in lymphocyte accumulation in B-CLL.

5/7/38 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE

07146742 EMBASE No: 1998036256
Elevated levels of biologically active soluble **CD40 ligand** in the serum of patients with chronic lymphocytic leukaemia
Younes A.; Snell V.; Consoli U.; Clodi K.; Zhao S.; Palmer J.L.; Thomas E.K.; Armitage R.J.; Andreeff M.
Dr. A. Younes, Section of Lymphoma, M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030 United States
British Journal of Haematology (BR. J. HAEMATOL.) (United Kingdom) 1998, 100/1 (135-141)
CODEN: BJHEA ISSN: 0007-1048
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 27

Chronic lymphocytic leukaemia (CLL) is an indolent lymphoproliferative disorder manifested by low growth fraction and prolonged survival of the malignant cells. The mechanisms that enable CLL cells to live longer and to resist apoptosis remain unclear. Because the malignant CLL cells express CD40 and Fas receptors, which can transduce cell-survival and cell-death signals, we examined the role of CD40 in the growth regulation of CLL cells and its interaction with Fas-mediated and fludarabine-induced apoptosis in vitro. Primary CLL cells underwent spontaneous apoptosis in culture, which was enhanced by exogenous human Fas ligand (FasL) or fludarabine. Exogenous **CD40L** rescued CLL cells from spontaneous apoptosis in a dose-dependent manner, and caused CLL cells to resist apoptosis induced by FasL or fludarabine. Patients' autologous plasma rescued CLL cells from spontaneous apoptosis, an effect that could be reversed with anti-**CD40 ligand** (**CD40L**) antibodies. The levels of soluble **CD40 ligand** in the sera of 51 CLL patients and 55 healthy donors were determined by enzyme-linked immunosorbent assay. The mean soluble **CD40L** level in normal donors was 0.29 ng/ml compared to a mean value of 0.80 ng/ml in CLL patients ($P < 0.001$). **CD40L** up-regulated bcl-XL mRNA but not bcl-2 in CLL cells within 3-6h in culture. Our results demonstrated that serum of patients with CLL contained elevated levels of biologically active soluble **CD40L**, and that **CD40L** can prolong survival of CLL cells and mediate their resistance to FasL and fludarabine in vitro.

5/7/34 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE

10662892 EMBASE No: 2000145741
CD40 ligand in CLL pathogenesis and therapy
Schattner E.J.
Dr. E.J. Schattner, Division Hematology Medical Oncology, Weill Medical College, 1300 York Avenue, New York, NY 10021 United States
AUTHOR EMAIL: ejsch@mail.med.cornell.edu
Leukemia and Lymphoma (LEUK. LYMPHOMA) (United Kingdom) 2000, 37/5-6 (461-472)
CODEN: LELYE ISSN: 1042-8194
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 113

Advances in immunology during the past three decades have facilitated our understanding of the biology of specific lymphoid neoplasms including chronic lymphocytic **leukemia** (CLL). Investigations in our laboratory have focused on CD40, a critical regulator of B cell survival and differentiation, and its ligand, CD154 (**CD40L**). We have established that in some cases of CLL the malignant cells express both CD40 and CD154, and on the basis of those observations, proposed a model for CLL tumor growth due to CD40-CD154 interactions within and among the malignant cells, and for the occurence of autoimmune syndromes in some cases of CLL. Here, we include an update on our studies regarding CD154 expression in CLL, a review of the data regarding the consequences of CD40 engagement in CLL B cells, and a discussion of these findings in the context of the complex and potentially opposite outcomes that have been reported for CD40-mediated signals in CLL. The implications for therapy, such as by impedance to CD154-CD40 interaction using antibody to CD154, or by selective inhibitors of NF-kappaB, are considered.

5/7/31 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

11040677 EMBASE No: 2001073341
Overview of idiopathic thrombocytopenic purpura: New approach to refractory patients
Bussel J.B.
Dr. J.B. Bussel, Weill Med. College of Cornell Univ., Department of Pediatrics, Div. of Pediatric Hematol./Oncology, 525 E 68th St, New York, NY 10021 United States
Seminars in Oncology (SEMIN. ONCOL.) (United States) 2000, 27/6 SUPPL. 12 (91-98)
CODEN: SOLGA ISSN: 0093-7754
DOCUMENT TYPE: Journal ; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 25

Idiopathic thrombocytopenic purpura is a disorder in which autoantibodies are made to platelets, resulting in accelerated platelet destruction. The diagnosis may be made in outpatients who are previously well or in patients with multiple medical conditions and medications. There are no unequivocal ways to distinguish immune thrombocytopenias from other thrombocytopenias, even with state-of-the-art tests including antiplatelet antibodies, thrombopoietin, glycocalicin, and platelet reticulocyte counts. Clinical evaluation includes ruling out a systemic process such as a viral infection or **leukemia**. **Treatment** of idiopathic thrombocytopenic purpura should be individualized. Substantial platelet increases are seen in more than 50% of patients who receive intravenous IgG, intravenous anti-D, steroids, or splenectomy. Two additional agents showing promising clinical trial experience are anti-**CD40 ligand** and rituximab (Rituxan; Genentech, Inc, South San Francisco, CA and IDEC Pharmaceutical Corporation, San Diego, CA). Copyright (c) 2000 by W.B. Saunders Company.

5/7/27 (Item 27 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10922564 BIOSIS NO.: 199799543709
Stimulation of B-chronic lymphocytic **leukemia** cells by murine fibroblasts, IL-4, anti-CD40 antibodies, and the soluble **CD40 ligand**.
AUTHOR: Buske Christian(a); Gogowski Gerald; Schreiber Karin; Rave-Fraenk Margret; Hiddemann Wolfgang; Woermann Bernhard
AUTHOR ADDRESS: (a)Dep. Internal Med., Div. Hematol./Oncol., Univ. Hosp., Robert-Koch-Str. 40, 37075 Goettingen**Germany
JOURNAL: Experimental Hematology (Charlottesville) 25 (4):p329-337 1997
ISSN: 0301-472X
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Analysis of growth regulation in B-chronic lymphocytic **leukemia** (B-CLL) is of pivotal importance for understanding the pathophysiology and the development of new **therapeutic** approaches. We investigated the effect of soluble ligands and the interaction with fibroblasts in an in vitro system developed for the expansion of normal B lymphocytes. A total of 17 peripheral blood and bone marrow samples from patients with untreated B-CLL were analyzed for survival, apoptosis, and bcl-2 protein expression. The most efficient stimulus for cell survival was cocultivation with CDw32-transfected murine fibroblasts, which achieved a median of 56% surviving CDS positive B cells with a plateau between Day 3 and Day 13 (p lt 0.0001). IL-4 alone had a significant, but less profound, effect on cell survival: cell viability was increased by a factor of 1.7 on Day 3 (p = 0.001), but cell viability continued to decline. In contrast, the soluble recombinant human **CD40 ligand** and two different anti-CD40 antibodies did not prolong cell survival. In all experiments prolongation of cell survival was accompanied by a significant reduction of apoptosis of the leukemic B cells: in CDw32-transfected fibroblasts apoptosis was reduced by a mean of 90%, in IL-4 by a mean of 55%. Reduction in apoptotic cell death was associated with elevated bcl-2 protein levels. Our results emphasize the critical role of the interaction between B-CLL cells and CDw32-transfected fibroblasts for cell viability in vitro. Prolongation of cell survival is caused by a reduction of apoptosis and correlates with bcl-2 protein expression.

5/7/25 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11119022 BIOSIS NO.: 199799740167
CD40 ligand induces an antileukemia immune response in vivo.
AUTHOR: Dilloo Dagmar; Brown Michael; Roskrow Marie; Zhong Wanyung; Holladay Martha; Holden William; Brenner Malcolm(a)
AUTHOR ADDRESS: (a)Cell Gene Therapy Program, St. Jude Children's Res. Hosp., 332 N. Lauderdale, Memphis, TN 38105**USA
JOURNAL: Blood 90 (5):p1927-1933 1997
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **Leukemia** cells may express tumor specific antigens in association with Class I and II major histocompatibility complex (MHC) molecules. However, lack of expression of conventional costimulator molecules means that these cells tend to induce specific T-cell energy rather than activation. **CD40 ligand** (**CD40L**) is a costimulator molecule that directly activates T cells and may promote antigen presentation by CD40-expressing cells, which include professional antigen presenting cells and B-acute lymphoblastic **leukemia** (ALL) cells from many patients. We determined whether transgenic expression of **CD40L** could enhance an antileukemia immune response using a CD40+ murine lymphoblastic (A20) **leukemia** and a CD40- myeloblastic (WEHI-3) **leukemia** in a tumor **treatment** model. Injection of otherwise nonimmunogenic A20 cells in the presence of **CD40L** induced an immune response active against preexisting A20 tumor at a distant site. Moreover, concomitant local secretion of transgenic interleukin-2 (IL-2) further amplified the antileukemic response induced and increased protection against preexisting tumor. In ex vivo studies, CD40 activation of A20 cells enhances the antigen presenting potential of A20 cells by upregulating expression of B7.1 (CD80), Class I and 11 MHC molecules, and increases expression of fas antigens. The importance of CD40 activation to the resulting antitumor response is further emphasized by the failure of transgenic **CD40L** to protect against the CD40- WEHI myeloblastic **leukemia**. Depletion studies showed the protective effects against A20 cells to be mediated by a combination of CD4+ and CD8+ T lymphocytes and by natural killer (NK) cells. These results suggest a means by which

(Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11870210 BIOSIS NO.: 199900116319
Inhibition of T cell/B cell interaction by B-CLL cells.
AUTHOR: Kneitz C; Goller M; Wilhelm M; Mehringer C; Wohlleben G; Schimpl A; Tony H-P
AUTHOR ADDRESS: Medizinische Poliklinik, Univ. Wuerzburg, Klinikstr. 6-8, D-97070 Wuerzburg**Germany
JOURNAL: Leukemia (Basingstoke) 13 (1):p98-104 Jan., 1999
ISSN: 0887-6924
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The course of disease in patients suffering from chronic lymphocytic **leukemia** (CLL) is determined by a profound dysregulation of the immune system. The resulting immune **suppression** is the main cause of death in those patients. In the present study we addressed the question of whether leukemic B cells (B-CLL) are able to suppress regular T cell/B cell interaction. Activated CD4+T cell clones induce expression of the early activation antigen CD23 on B lymphocytes in vitro. Under conditions used, this B cell activation event was dependent upon direct T cell contact. Addition of certain bystander B-CLL cells or normal B lymphocytes resulted in a cell number-dependent inhibition of B cell induction. This seems to reflect the competition of B-CLL cells for a cell contact-mediated T cell helper signal. By using **CD40 ligand** transfected fibroblasts as a substitute for T cell help, we show that the same B-CLL cells also suppress **CD40 ligand**-mediated B cell activation. B-CLL cells differ in their ability to inhibit **CD40 ligand**-mediated B cell activation. Some B-CLL cases (eight out of 14) are unable to compete for the T cell or **CD40 ligand**-mediated signal, even though they can functionally interact with **CD40 ligand** and thereby get activated themselves. In addition, these results indicate that the observed inhibition is not a result of cell crowding by merely reducing the chance of specific B cell/T cell interactions. Collectively, these data indicate that B-CLL cells are able to inhibit the interaction of activated T lymphocytes with normal B lymphocytes in vitro. Perturbed T cell/B cell interaction may represent an important mechanism underlying the various defects of the specific immune system observed in patients

5/7/20 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12285753 BIOSIS NO.: 200000043620
A phase I study of CD154 (**CD40-ligand**) gene **therapy** for chronic lymphocytic **leukemia**.
AUTHOR: Wierda W G(a); Rassenti L Z(a); Cantwell M J(a); Woods S J(a); Kipps T J(a)
AUTHOR ADDRESS: (a)Division of Hematology/Oncology, UCSD Human Gene Therapy Program, Dept. of Medicine, UCSD School of Medicine, La Jolla, CA**USA
JOURNAL: Blood 94 (10 SUPPL. 1 PART 1):p602a Nov. 15, 1999
CONFERENCE/MEETING: Forty-first Annual Meeting of the American Society of Hematology New Orleans, Louisiana, USA December 3-7, 1999
SPONSOR: The American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Citation

13092862 BIOSIS NO.: 200100300011
Optimal culture conditions of **CD40L**-stimulated B-lineage acute lymphoblastic **leukemia** (ALL) cells: A prerequisite to develop a strategy for a vaccine **therapy**.
AUTHOR: Gaipa Giuseppe(a); Todisco Elisabetta(a); Roth Teresa(a); Balduzzi Adriana(a); Golay Jose; Introna Martino; Biondi Andrea(a)
AUTHOR ADDRESS: (a)Ospedale San Gerardo, Clinica Pediatrica Universita' di Milano Bicocca, Monza**Italy
JOURNAL: Blood 96 (11 Part 2):p211b November 16, 2000
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000
SPONSOR: American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Enhancement of the antigen presenting cell (APC) capacity of ALL cells, can be developed into a strategy for a vaccine therapy. So far it has been shown that CD40-cross-linking on ALL cells by NIH3T3 transfected with the **CD40L** coding region or by soluble **CD40L** (fusion protein of murine **CD40L** and CD8a chain) can induce expression of B7-family members (B7-1/CD80; B7-2/CD86) and generation of autologous anti-ALL-specific cytolytic T-cell lines (Cardoso et al Blood 1997) that could be used for adoptive immunotherapy. Conceivably, irradiated ALL cells, rendered capable to present antigen, could be able to induce a host anti-**leukemia** immune response when administered to patients with a minimal residual disease. In the perspective of using **CD40L** -stimulated ALL cells in a clinical setting, we used a trimeric soluble **CD40 Ligand** (sCD40L) molecule (Alexis) and human bone marrow stroma (HBMS) to support ALL cells viability. Thawed cells, frozen at diagnosis, from 10 ALL children were cultured on HBMS in presence of sCD40L. Cell viability after 48h of culture on HMBS was high (mean 83%, range 54% - 103%). Compared to the control culture (HBMS without sCD40L), addition of sCD40L induced up-regulation of CD86 expression in 7 of 10 cases (mean percent of positive ALL cells: 48% versus 22%) and up-regulation of CD80 in 4 of 10 cases (52%, 72%, 80% and 36% versus 2%, 11%, 3% and 3%) and a slight up-regulation of CD40 in 5 of 5 cases (mean 61% versus 49%). By contrast, cell viability in cultures without stroma was poor (mean 15%) and **CD40L** did not up-regulate CD80 and CD86 on the few ALL cells surviving after 48h of culture. To investigate the effect of HBMS on the modulation of these molecules, we also compared the expression level of CD86, CD80 and CD40 one hour after thawing and after 48 hours culture on HBMS in absence of **CD40L**: HBMS increased the expression of CD86 in 6 of 14 cases (mean 14% to 31%), of CD40 in 8 of 9 cases (mean 29% to 56%) and in 1 case, induced expression of CD80 (negative to 11%). Our data indicate that the culture of ALL cells on HBMS in presence of sCD40L modifies the ALL cells APC capacity and preserves their viability thus making them potentially available for

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Set     Items   Description
S1        367   (CD40L OR CD40(W)LIGAND) AND LEUKEMIA?
S2        128   S1 AND (TREAT? OR THERAP?)
S3         86   RD S2 (unique items)
S4         89   S1 AND (INHIBIT? OR SUPPRESS? OR TREAT? OR THERAP? OR ANTA-
                  GONI?)(20N)(LEUKEMIA?)
S5         65   RD S4 (unique items)
? s s1 and review?

             367  S1
         3023130  REVIEW?
      S6      14  S1 AND REVIEW?
? rd s6

...completed examining records
      S7      11  RD S6 (unique items)
? t s7/7/all


 7/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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11584052   BIOSIS NO.: 199800364748
Programmed cell death: The influence of CD40, CD95 (Fas or Apo-I) and their
  ligands.
AUTHOR: Laytragoon-Lewin N(a)
AUTHOR ADDRESS: (a)Immune Gene Therapy Lab., Dep. Oncol., Radiumhemmet,
  Karolinska Hosp., S-17176 Stockholm**Sweden
JOURNAL: Medical Oncology (Basingstoke)  15 (1):p15-19 April, 1998
ISSN: 1357-0560
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Programmed cell death (PCD) or apoptosis is a process whereby
  developmental or environmental stimuli activate a specific series of
  events that culminate in cell death. PCD is essential for normal
  development and abnormality in the process can lead to defects ranging
  from embryonic lethality and tissue-specific perturbation of postnatal
  development to a high susceptibility to malignancy. Therapeutics that
  modulate the regulation of PCD may provide a new opportunity for the
  treatment of the PCD related diseases and cancer. CD40 and CD95
  (Fas/Apo-I) are transmembrane proteins of the nerve growth factor/tumour
  necrosis factor alpha receptor superfamily. The death signal of PCD
  occurs when the CD95 receptor on the cell surface binds to the CD95
  ligand (CD95L) or to the anti-CD95 monoclonal antibody (mAb). In
  contrast, PCD could be inhibited by the survival signal mediated from the
  binding of the CD40 receptor to the CD40 ligand (CD40L)
  or to the anti-CD40 mAb. In this review, the interaction of CD40/
  CD40L and CD95/CD95L on PCD in normal and malignant cells is
  discussed.


 7/7/2     (Item 1 from file: 73)
DIALOG(R)File  73:EMBASE
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11195471 EMBASE No: 2001206104
CD40 ligand (CD154) and tumour necrosis factor-related apoptosis inducing ligand (Apo-2L) in haematological malignancies
Fiumara P.; Younes A.
Dr. A. Younes, Department of Lymphoma, Univ. TX M.D. Anderson Cancer Ctr., 1515 Holcombe Boulevard, Houston, TX 77030 United States
AUTHOR EMAIL: ayounes@mail.mdanderson.org
British Journal of Haematology (BR. J. HAEMATOL.) (United Kingdom) 2001, 113/2 (265-274)
CODEN: BJHEA ISSN: 0007-1048
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 107

7/7/3 (Item 2 from file: 73)

11150636 EMBASE No: 2001164778
Contribution of nitric oxide to the apoptotic process in human B cell chronic lymphocytic leukaemia
Kolb J.-P.; Roman V.; Mentz F.; Zhao H.; Rouillard D.; Dugas N.; Dugas B.; Sigaux F.
J.-P. Kolb, U365 INSERM, Institute Curie, Hopital Pitie Salpetriere, 26 rue d'Ulm, 75231 Paris Cedex 05 France
AUTHOR EMAIL: jpkolb@curie.fr
Leukemia and Lymphoma (LEUK. LYMPHOMA) (United Kingdom) 2001, 40/3-4 (243-257)
CODEN: LELYE ISSN: 1042-8194
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 51

B cell chronic lymphocytic leukaemia (B-CLL) is characterised by defective apoptosis that cannot be explained solely on the basis of the known chromosomal abnormalities. We and other have now reported that the leukemic cells spontaneously display the inducible isoform of nitric oxide synthase, iNOS. Inhibition of the iNOS pathway leads to increased apoptosis of the tumoral cells in vitro, indicating that the endogenous release of NO contributes to their resistance to the normal apoptotic process. The factors that induce the expression of iNOS in vivo in the leukemic cells are not yet identified. Yet, as interaction of B-CLL leukemic cells with bone marrow stromal cells promotes their survival, the involvement of adhesion molecules and integrins may be suspected. The engagement of CD23 stimulates iNOS activation in the tumoral cells, suggesting that in vivo interaction of CD23 with one of its recognised ligands may contribute to iNOS induction. A role for CD40-**CD40 ligand** interaction may also be hypothesised. The mechanisms involved in the anti-apoptotic role of NO are not fully understood, but may implicate the inhibition of caspase activity, hence the impairment of the Fas pathway. In addition, the mitochondrial membrane potential disruption appears to be a NO-sensitive step in the apoptosis cascade. The presence of a NOS displaying anti-apoptotic properties has now been recognised in different cell types, including various leukaemia. A better knowledge of the mechanisms governing the ultimate fate of NO, anti- versus pro-apoptotic would allow the development of new therapeutic approaches for the treatment of these diseases.

7/7/4 (Item 3 from file: 73)

10662892 EMBASE No: 2000145741

CD40 ligand in CLL pathogenesis and therapy
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Dr. E.J. Schattner, Division Hematology Medical Oncology, Weill Medical College, 1300 York Avenue, New York, NY 10021 United States
AUTHOR EMAIL: ejsch@mail.med.cornell.edu
Leukemia and Lymphoma (LEUK. LYMPHOMA) (United Kingdom) 2000, 37/5-6 (461-472)
CODEN: LELYE ISSN: 1042-8194
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 113

Advances in immunology during the past three decades have facilitated our understanding of the biology of specific lymphoid neoplasms including chronic lymphocytic **leukemia** (CLL). Investigations in our laboratory have focused on CD40, a critical regulator of B cell survival and differentiation, and its ligand, CD154 (**CD40L**). We have established that in some cases of CLL the malignant cells express both CD40 and CD154, and on the basis of those observations, proposed a model for CLL tumor growth due to CD40-CD154 interactions within and among the malignant cells, and for the occurence of autoimmune syndromes in some cases of CLL. Here, we include an update on our studies regarding CD154 expression in CLL, a **review** of the data regarding the consequences of CD40 engagement in CLL B cells, and a discussion of these findings in the context of the complex and potentially opposite outcomes that have been reported for CD40-mediated signals in CLL. The implications for therapy, such as by impedance to CD154-CD40 interaction using antibody to CD154, or by selective inhibitors of NF-kappaB, are considered.

7/7/5 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

07716347 EMBASE No: 1999208990
Cytotoxic T lymphocytes to endogenous mouse retroviruses and mechanisms of retroviral escape
Green W.R.
W.R. Green, Dartmouth Medical School, Department of Microbiology, 6W Borwell Building, One Medical Center Drive, Lebanon, NH 03756 United States
AUTHOR EMAIL: william.r.green@dartmouth.edu
Immunological Reviews (IMMUNOL. REV.) (Denmark) 1999, 168/- (271-286)
CODEN: IMRED ISSN: 0105-2896
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 93

Mouse retrovirus-induced lymphoma/**leukemia** and immunodeficiency are useful models for analogous human diseases. Both ecotropic (mouse tropic) and recombinant retroviruses, including the polytropic mink cytopathic focus-inducing type, have been studied for disease pathogenesis and as targets for humoral and cellular immunity, particularly cytotoxic T-lymphocyte (CTL) responses. For AKR/Gross murine **leukemia** viruses (MuLV) we have defined an immunodominant CTL epitope in the p1 5E transmembrane anchor envelope protein and three minor/subdominant epitopes. Evidence is presented for retroviral escape from CTL by selection following genetic recombination and point mutation both within and outside CTL epitope sequences, and via endogenous retrovirus-infected cell downregulation of the generation of anti-AKR/Gross MuLV CTL. As demonstrated in vivo in naturally occurring non-responder strains bp adoptive transfer, and in vitro by cell mixing experiments, a central non-responsiveness mechanism appears to be peripheral inhibition mediated by infected cells expressing MHC-presented viral peptides. Such inhibition requires Fas expression by antiviral T cells; occurs upon TCR-mediated recognition of virus-infected, Fas ligand-expressing 'veto' cells; and

apparently leads to an antigen-specific form of activation-induced cell death of T cells. In the LP-BM5 MuLV isolate that causes murine AIDS (MAIDS) retroviral variation also leads to CTL escape - the BM5-helper virus has altered forms of the immunodominant and two minor/subdominant epitopes. In contrast, a novel immunodominant CTL epitope is recognized by MAIDS-resistant, but not MAIDS-susceptible, strains. This epitope is uniquely encoded in an alternative translational reading frame of the viral gag gene. It also appears that the LP-BM5 MuLV have co-opted the cells of the immune system for retroviral pathogenesis - CD40/**CD40L** (CD 154) interactions are required both for the initiation and progression of MAIDS.

7/7/6 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

07557481 EMBASE No: 1999053020
CD5 B cells and B-cell malignancies
Lydyard P.M.; Jewell A.P.; Jamin C.; Youinou P.Y.
Dr. P.M. Lydyard, Department of Immunology, UCL Medical School, London United Kingdom
Current Opinion in Hematology (CURR. OPIN. HEMATOL.) (United States) 1999, 6/1 (30-36)
CODEN: COHEF ISSN: 1065-6251
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 107

Over the past year, progress has been made in understanding of the physiology and disease associations of CD5+ (B1) B cells, although their exact role in pathogenesis remains unclear. Earlier studies on the negative function of CD5 within the B-cell receptor complex have been substantiated, and it seems likely that soon the signaling pathways used by this coreceptor will be elucidated. Progress in diagnosis, physiology, and etiopathogenesis of CD5+ malignancies has been made, particularly in B-cell chronic lymphocytic **leukemia**. The low-level expression of surface immunoglobulin has been explained by the mutations that occur in the associated CD79b. Two new potential tumor-suppressor genes have been identified in the hot spot of chromosome 13q, which provides an exciting step forward in understanding of the etiopathogenesis of some B-cell chronic lymphocytic **leukemia**. Activated signal transducers for activation of transcription factors molecules have been shown to be phosphorylated on different amino acids in B1 and chronic lymphocytic **leukemia** tumors, although the significance of this is, as yet, unclear. Finally, aberrant expression of **CD40L** by chronic lymphocytic **leukemia** T cells may contribute to the immunodeficiency that develops in these patients.

7/7/7 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

06844998 EMBASE No: 1997127554
CD40/**CD40 ligand** interactions in normal, reactive and malignant lympho-hematopoietic tissues
Gruss H.-J.; Herrmann F.; Gattei V.; Gloghini A.; Pinto A.; Carbone A.
H.-J. Gruss, Department of Internal Medicine III, Lymphoma Biology Laboratory, University of Ulm Medical Center, Robert-Koch-Str. 8, D-89081 Ulm-Donau Germany
Leukemia and Lymphoma (LEUK. LYMPHOMA) (United Kingdom) 1997, 24/5-6 (393-422)
CODEN: LELYE ISSN: 1042-8194
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 236

7/7/8 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09082763 96416165 PMID: 8819071
The role of the CD40 antigen on malignant B cells.
Planken EV; Willemze R; Kluin-Nelemans JC
Department of Hematology, Leiden University Hospital, The Netherlands.
Leukemia & lymphoma (SWITZERLAND) Jul 1996, 22 (3-4) p229-35, ISSN 1042-8194 Journal Code: BNQ
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed
An increasing amount of literature has been published concerning the interaction of the CD40 antigen and its ligand with regard to normal B cell ontogeny. In this **review**, an overview of the CD40 antigen and the **CD40 ligand** is given, focussing on their possible role in B cell malignancies. Data on the expression of the CD40 antigen on various B cell malignancies (acute and chronic **leukemias** , non-Hodgkin's lymphoma and multiple myeloma) are presented. The recently developed novel culture "CD40 system" is described. This system is a powerful tool used to culture normal B cells, but also most malignant B cells. We demonstrate in addition a more prominent role of the human Fc receptor presenting murine fibroblasts in the "CD40 system", especially in relation to cultured plasma cells. Finally, some important applications of the "CD40 system" are also summarized. (63 Refs.)
Record Date Created: 19970116

7/7/9 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

135151176 CA: 135(11)151176u JOURNAL
Immuno gene therapy of leukemia
AUTHOR(S): Kato, Kazunori
LOCATION: Dept. of Pharmacology, National Cancer Center, Japan,
JOURNAL: Igaku no Ayumi DATE: 2000 VOLUME: 195 NUMBER: 1 PAGES: 43-49
CODEN: IGAYAY ISSN: 0039-2359 LANGUAGE: Japanese PUBLISHER: Ishiyaku Shuppan
SECTION:
CA215000 Immunochemistry
CA214XXX Mammalian Pathological Biochemistry
IDENTIFIERS: review CD40 ligand gene therapy B cell leukemia
DESCRIPTORS:
T cell(lymphocyte)...
activation; CD40 ligand gene therapy of B-cell chronic lymphocytic leukemia in relation to
Gene therapy...
CD40 ligand gene therapy of B-cell chronic lymphocytic leukemia
Glycoproteins,specific or class...
CD40-L (antigen CD40 ligand); CD40 ligand gene therapy of B-cell chronic lymphocytic leukemia
Leukemia...
chronic B-lymphocytic; CD40 ligand gene therapy of B-cell chronic lymphocytic leukemia

7/7/10 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

135044805 CA: 135(4)44805b JOURNAL
Immuno gene therapy by CD40 ligand
AUTHOR(S): Kato, Kazunori

LOCATION: Pharmacology Division, National Cancer Center Research Institute, Japan,
JOURNAL: Igaku no Ayumi DATE: 2000 VOLUME: 194 NUMBER: 14 PAGES: 1261-1266 CODEN: IGAYAY ISSN: 0039-2359 LANGUAGE: Japanese PUBLISHER: Ishiyaku Shuppan
SECTION:
CA215000 Immunochemistry
CA214XXX Mammalian Pathological Biochemistry
IDENTIFIERS: review cancer therapy CD40 ligand chronic lymphocytic leukemia
DESCRIPTORS:
Glycoproteins,specific or class...
CD40-L (antigen CD40 ligand); immuno gene therapy with CD40 ligand against B-chronic lymphocytic leukemia
Leukemia...
chronic B-lymphocytic; immuno gene therapy with CD40 ligand against B-chronic lymphocytic leukemia
Antitumor agents... Gene therapy...
immuno gene therapy with CD40 ligand against B-chronic lymphocytic leukemia

7/7/11 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

132234890 CA: 132(18)234890m JOURNAL
CD30/CD30 ligand and CD40/CD40 ligand in malignant lymphoid disorders
AUTHOR(S): Younes, A.; Carbone, A.
LOCATION: Department of Lymphoma, U.T. M.D. Anderson Cancer Center, Houston, TX, USA
JOURNAL: Int. J. Biol. Markers DATE: 1999 VOLUME: 14 NUMBER: 3
PAGES: 135-143 CODEN: IBMAEP ISSN: 0393-6155 LANGUAGE: English
PUBLISHER: Wichtig Editore
SECTION:
CA214000 Mammalian Pathological Biochemistry
CA215XXX Immunochemistry
IDENTIFIERS: CD30 CD30L CD40 CD40L lymphoid neoplasm review
DESCRIPTORS:
Antigens...
CD30 ligand; CD30/CD30 ligand and CD40/CD40 ligand in malignant lymphoid disorders
CD30(antigen)... CD40(antigen)... Leukemia... Lymphoma...
CD30/CD30 ligand and CD40/CD40 ligand in malignant lymphoid disorders
Glycoproteins,specific or class...
CD40-L (antigen CD40 ligand); CD30/CD30 ligand and CD40/CD40 ligand in malignant lymphoid disorders

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 s s1 and py=1996

             367  S1
         2048977  PY=1996
      S8      22  S1 AND PY=1996
? rd s8

...completed examining records
      S9      15  RD S8 (unique items)
? t s9/7/all


 9/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10770628   BIOSIS NO.: 199799391773
B-CLL cells differ in their ability to disturb T-cell/B-cell interaction.
AUTHOR: Kneitz C(a); Schimpl A; Mehringer C; Wilhelm M; Tony H P
AUTHOR ADDRESS: (a)Med. Poliklinik Univ. Wuerzburg, Wuerzburg**Germany
JOURNAL: Annals of Hematology  73 (SUPPL. 2):pA131 1996
CONFERENCE/MEETING: Annual Congress of the German and the Austrian Society
of Hematology and Oncology  Duesseldorf, Germany  October 3-7, 1996
ISSN: 0939-5555
RECORD TYPE: Citation
LANGUAGE: English


 9/7/2     (Item 2 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10770627   BIOSIS NO.: 199799391772
CD40/CD40 ligand interactions in reactive and malignant
  lympho-hematopoietic tissues.
AUTHOR: Gruss Hans-Juergen(a); Pinto Antonio; Carbone Antonino; Herrmann
  Friedhelm
AUTHOR ADDRESS: (a)Dep. Internal Med. III, Univ. Ulm Med. Cent., D-89081
  Ulm**Germany
JOURNAL: Annals of Hematology  73 (SUPPL. 2):pA131 1996
CONFERENCE/MEETING: Annual Congress of the German and the Austrian Society
of Hematology and Oncology  Duesseldorf, Germany  October 3-7, 1996
ISSN: 0939-5555
RECORD TYPE: Citation
LANGUAGE: English


 9/7/3     (Item 3 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10734646   BIOSIS NO.: 199799355791
Chronic lymphocytic leukemia B cells express CD40L and
  demonstrate T cell type costimulatory capacity.
AUTHOR: Schattner Elaine J(a); Mascarenhas John; Koshy Mary; Vakkalanka
  Radha K; Friedman Steven M; Crow Mary K
AUTHOR ADDRESS: (a)Division Hematol./Oncol., Dep. Med., New York Hosp.
  Cornell Med. Cent., Division Rheumatol., Hos**USA
JOURNAL: Blood  88 (10 SUPPL. 1 PART 1-2):p218B 1996
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of
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Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

9/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10733653 BIOSIS NO.: 199799354798
Occurrence of thymic lymphoblastic lymphoma in **CD40 ligand** knock-out mice transplanted with bone marrow cells expressing retrovirally transduced **CD40 ligand**.
AUTHOR: Brown M P; Zhao J F; Brenner M K
AUTHOR ADDRESS: Cell Gene Therapy Program, St. Jude Children's Res. Hosp., Memphis, TN**USA
JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p654A **1996**
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

9/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10732221 BIOSIS NO.: 199799353366
Acquired **CD40-ligand** deficiency in patients with B cell chronic lymphocytic **leukemia**.
AUTHOR: Cantwell M J; Hua T; Pappas J; Kipps T J
AUTHOR ADDRESS: Div. Hematology Oncology, UCSD Cancer Cent., UCSD Sch. Med., La Jolla, CA**USA
JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p296A **1996**
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

9/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10732136 BIOSIS NO.: 199799353281
CD40 ligand acts as a co-stimulator molecule for the generation of an anti-leukemic immune response and its activity is enhanced by interleukin-2 (IL-2).
AUTHOR: Dilloo D; Brown M; Zhong W; Holladay M; Brenner M
AUTHOR ADDRESS: St. Jude Children's Res. Hosp., Memphis, TN**USA
JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p275A **1996**
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

9/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10731979 BIOSIS NO.: 199799353124

CD40 ligand rescues chronic lymphocytic **leukemia** (CLL) cells from spontaneous apoptosis and mediates resistance to FAS ligand and fludarabine.
AUTHOR: Younes A(a); Snell V; Consoli U; Clodi K; Thomas E K; Andreeff M
AUTHOR ADDRESS: (a)Dep. Hematol., U.T.M.D. Anderson Cancer Cent., Houston, TX**USA
JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p236A **1996**
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

9/7/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10692218 BIOSIS NO.: 199799313363
In vitro expansion and characterization of dendritic cells derived from human bone marrow CD34+ cells.
AUTHOR: Ye Z; Gee A P(a); Bowers W E; Lamb L S; Turner M W; Henslee-Downey P J
AUTHOR ADDRESS: (a)Div. Transplantation Med., Applied Res. Program, Univ. S.C. and Richland Meml. Hosp., 7 Richland**USA
JOURNAL: Bone Marrow Transplantation 18 (5):p997-1008 **1996**
ISSN: 0268-3369
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Dendritic cells (DC), as professional antigen-presenting cells, play a major role in stimulating naive T cell responses in vivo and in vitro, and may exacerbate or modulate T lymphocyte-mediated reactions, such as interactions between a hematopoietic graft and the recipient, e.g. GVHD and graft-versus-**leukemia**. Here, we describe a two-stage cell culture system for expansion of functionally active human DC from CD34+ marrow precursors. Optimal outgrowth was achieved by initially culturing CD34+ cells for 5 days in medium containing GM-CSF, MGF and TNF-alpha. Substitution of **CD40L** and IL-4 for TNF-alpha during a subsequent 5-day subculture increased DC content, such that by 10 days the cultures contained approximately 40% DC as determined by immunophenotype and morphology. An increase in DC purity to 84% at 10 days was achieved by immunomagnetic separation for CD1a+ cells from 5-day cultures and subculturing these cells in medium with IL-4 and **CD40L** . Reversing the sequence of growth factors during culture and subculture decreased the yield and purity of DC. Expression of CD80 and CD86 was enhanced by adding **CD40L** and IL-4, and the DC showed stimulatory activity in MLC. In conclusion, we have described a simple two-stage culture system to generate functional DC from CD34+ marrow precursors.

9/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10664771 BIOSIS NO.: 199799285916
Proliferation of precursor B-lineage acute lymphoblastic leukaemia by activating the CD40 antigen.
AUTHOR: Planken E V(a); Dijkstra N H; Bakkus M; Willemze R; Kluin-Nelemans J C
AUTHOR ADDRESS: (a)Dep. Haematology, Bldg 1, C2-R, Rijnsburgerweg 10, 2333 AA Leiden**Netherlands
JOURNAL: British Journal of Haematology 95 (2):p319-326 **1996**
ISSN: 0007-1048
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: No reliable culture system exists for B-lineage acute lymphoblastic leukaemia (ALL). Recently we found that many different mature B-cell malignancies proliferate upon stimulation via the CD40 antigen, and this led us to investigate whether a similar CD40 activation on ALL cells could also induce proliferation. First, we measured CD40 expression in 21 ALL cases; all were CD40+, although mostly weak. Next, we triggered the CD40 antigen by antiCD40 antibodies and by a **CD40 ligand**-expressing cell line. In addition, we measured the influence of IL-3, IL-4 and IL-7 with and without these stimuli. In 8/10 cases proliferation, measured by 3H-thymidine incorporation, could be induced after CD40 crosslinking, especially in the presence of IL-3. Stimulation via the **CD40 ligand** was more successful than using crosslinked antiCD40 antibodies. IL-4 inhibited the spontaneous proliferation found in three cases, but stimulated proliferation after CD40 crosslinking. IL-7 did not contribute to proliferation. Morphology, immunophenotyping and surface marker analysis, combined with DNA flow cytometry confirmed that the proliferation found could be ascribed to the ALL cells. In conclusion, B-lineage ALL cases are CD40+, and many can be cultured using CD40 stimulation and IL-3.

9/7/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10435997 BIOSIS NO.: 199699057142
Demonstration of functional CD40 in B-lineage acute lymphoblastic **leukemia** cells in response to T-cell **CD40 ligand.**
AUTHOR: Renard Nathalie; Lafage-Pochitaloff Marina; Durand Isabelle; Duvert Valerie; Coignet Lionel; Banchereau Jacques; Saeland Sem(a)
AUTHOR ADDRESS: (a)Schering-Plough Lab. Immunol. Res., 27 chemin des Peupliers, 69571 Dardilly**France
JOURNAL: Blood 87 (12):p5162-5170 **1996**
ISSN: 0006-4971
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Because activated T cells were previously shown to induce proliferation of human normal B-cell precursors (BCP) via the CD40 pathway, we investigated the effects of T cells on leukemic blasts isolated from patients with B-lineage acute lymphoblastic **leukemia** (BCP-ALL). An anti-CD3 activated human CD4+ T-cell clone was found to induce significant cell proliferation in four of nine BCP-ALL samples analyzed. In one of these cases,the T-cell effect was clearly dependent on interaction between CD40 and its ligand. Accordingly, a more thorough analysis was performed on this particular **leukemia** (case 461, adult early pre-B-ALL, mBCR+, Philadelphia+, i(9q)+). Thus, autologous CD4+ T cells isolated from the patient were also able to induce CD40-dependent proliferation of the leukemic blasts. Analysis of the phenotype after coculture showed that, among the CD19+ cells, a proportion gradually lost expression of CD10 and CD34, whereas some cells acquired CD23. In addition, and in contrast with normal BCP, activated T cells promoted maturation of a subset of the case 461 leukemic cells into surface IgM+ cells. The leukemic origin of the cycling and the maturing cells was assessed by the presence of i(9q), a chromosomal abnormality associated with this **leukemia** and evidenced by fluorescence in situ hybridization. Taken together, these results show that leukemic BCP can be activated via CD40 but that not all cases display detectable stimulation in response to T cells despite their expression of CD40. In addition, the present data suggest that CD4+ T cells could potentially play a role in the physiology of BCP-ALL.

9/7/11 (Item 1 from file: 73)

DIALOG(R)File 73:EMBASE

06695250 EMBASE No: 1996360187
In vitro expansion and characterization of dendritic cells derived from human bone marrow CD34sup + cells
Ye Z.; Gee A.P.; Bowers W.E.; Lamb L.S.; Turner M.W.; Henslee-Downey P.J.
Division of Transplantation Medicine, University of South Carolina, Richland Memorial Hospital, 7 Richland Medical Park,Columbia, SC 29203 United States
Bone Marrow Transplantation (BONE MARROW TRANSPLANT.) (United Kingdom) 1996, 18/5 (997-1008)
CODEN: BMTRE ISSN: 0268-3369
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Dendritic cells (DC), as professional antigen-presenting cells, play a major role in stimulating naive T cell responses in vivo and in vitro, and may exacerbate or modulate T lymphocyte-mediated reactions, such as interactions between a hematopoietic graft and the recipient, eg GVHD and graft-versus-**leukemia**. Here, we describe a two-stage cell culture system for expansion of functionally active human DC from CD34sup + marrow precursors. Optimal outgrowth was achieved by initially culturing CD34sup + cells for 5 days in medium containing GM-CSF, MGF and TNF-alpha. Substitution of **CD40L** and IL-4 for TNF-alpha during a subsequent 5-day subculture increased DC content, such that by 10 days the cultures contained approximately 40% DC as determined by immunophenotype and morphology. An increase in DC purity to 84% at 10 days was achieved by immunomagnetic separation for CDlasup + cells from 5 day cultures and subculturing these cells in medium with IL-4 and **CD40L**. Reversing the sequence of growth factors during culture and subculture decreased the yield and purity of DC. Expression of CD80 and CD86 was enhanced by adding **CD40L** and IL-4, and the DC showed stimulatory activity in MLC. In conclusion, we have described a simple two-stage culture system to generate functional DC from CD34sup + marrow precursors.

9/7/12 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

06590562 EMBASE No: 1996255221
CD4sup + T-cell induction of Fas-mediated apoptosis in Burkitt's lymphoma B cells
Schattner E.J.; Mascarenhas J.; Bishop J.; Yoo D.-H.; Chadburn A.; Crow M.K.; Friedman S.M.
Division of Hematology-Oncology, New York Hospital, 525 E 68th St,New York, NY 10021 United States
Blood (BLOOD) (United States) 1996, 88/4 (1375-1382)
CODEN: BLOOA ISSN: 0006-4971
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Cytotoxic function of CD4sup + T(h1) cells is mediated by Fas (CD95, APO-1) and its ligand (Fas ligand). Recent studies using nontransformed B cells and the Rámos Burkitt's lymphoma (BL) B-cell line cells show that CD40 ligation at the B-cell surface by activated, **CD40 ligand** (CD4OL)-bearing, CD4sup + T cells upregulates Fas expression on B cells and primes B cells for Fas-mediated death signals. In this work, we examine whether this CD4sup + T- cell-dependent molecular pathway for Fas upregulation and B-cell apoptosis reflects a peculiarity of the Ramos B-cell line or is applicable to other Burkitt's tumors as well. In 5 of the 6 Epstein-Barr virus-negative BL cell tines examined, the cells constitutively express undetectable or low levels of Fas and are resistant to Fas-mediated signals induced by monoclonal anti- Fas anti-body. All 6 of the BL cell line B cells upregulate Fas in response to CD40 ligation, and

in 4 of the cases they become sensitive to Fas-mediated death signals. In one BL cell line, the cells are constitutively sensitive to Fas-mediated cytolysis and are unaffected by CD40 signals. Next, we applied these immunologic manipulations to cells from a refractory clinical sample and observed that the tumor cells could be induced to express Fas and undergo apoptosis in our system. These results establish CD4sup + T cells and the Fas- Fas ligand system as important immune regulators of Burkitt's lymphoma B cells and indicate that the susceptibility of tumor cells to Fas-mediated death signals can be modulated by specific activation events at the cell surface.

9/7/13 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

06478241 EMBASE No: 1996144410
CD40 expressed on thymic epithelial cells provides costimulation for proliferation but not for apoptosis of human thymocytes
Ruggiero G.; Caceres E.M.; Voordouw A.; Noteboom E.; Graf D.; Kroczek R.A.; Spits H.
Division of Immunology, Netherlands Cancer Institute, Plesmanlaan 121,1066 CX, Amsterdam Netherlands
Journal of Immunology (J. IMMUNOL.) (United States) 1996, 156/10 (3737-3746)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Human thymic epithelial cells express CD40, so we examined the possible role of CD40 in activation of thymocytes. We observed that both CD4sup +CD8sup - and CD4sup -CD8sup + thymocytes proliferate after stimulation by anti-CD3 mAb in the presence of cultured thymic epithelial cells. Costimulation of CD4sup + thymocytes by thymic epithelial cells is partly inhibited by an anti-CD40 mAb, but this mAb has no effect on costimulation of CD8sup + thymocytes. The selective costimulatory ability of CD40 for CD4sup + thymocytes was confirmed in experiments in which thymocytes were stimulated with anti-CD3 in the presence of murine P815 cells transfected with CD40 cDNA. The level of costimulation induced by P815-CD40 was comparable with that induced by P815 cells expressing CD80 (B7.1). Treatment of thymocytes with the Casup 2sup + ionophore ionomycin and the phorbolester PMA or with anti-CD3 mAb resulted in up- regulation of the **CD40 ligand**, suggesting that this molecule is involved in CD40-mediated costimulation of human thymocytes. Costimulation of thymocytes by CD80 strongly increased anti-CD3-induced death of fetal thymocytes. In contrast, costimulation by CD40 did not increase anti-CD3-mediated apoptosis of these thymocytes. To confirm that CD40 does not affect anti-CD3-induced cell death, we established a variant of the Jurkat T leukemic cell line that constitutively expresses **CD40L** and analyzed the sensitivity of this cell line for activation-induced apoptosis. In contrast to CD80, CD40 failed to increase anti-CD3-mediated apoptosis in CD40Lsup + Jurkat cells, whereas both CD40 and CD80 strongly increased IL-2 production induced by anti-CD3. These findings suggest that costimulation by CD40 is involved in clonal expansion of CD4sup + thymocytes but not in activation-induced cell death.

9/7/14 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09082763 96416165 PMID: 8819071
The role of the CD40 antigen on malignant B cells.
Planken EV; Willemze R; Kluin-Nelemans JC
Department of Hematology, Leiden University Hospital, The Netherlands.
Leukemia & lymphoma (SWITZERLAND) Jul **1996**, 22 (3-4) p229-35, ISSN 1042-8194 Journal Code: BNQ

Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed
An increasing amount of literature has been published concerning the interaction of the CD40 antigen and its ligand with regard to normal B cell ontogeny. In this review, an overview of the CD40 antigen and the **CD40 ligand** is given, focussing on their possible role in B cell malignancies. Data on the expression of the CD40 antigen on various B cell malignancies (acute and chronic **leukemias** , non-Hodgkin's lymphoma and multiple myeloma) are presented. The recently developed novel culture "CD40 system" is described. This system is a powerful tool used to culture normal B cells, but also most malignant B cells. We demonstrate in addition a more prominent role of the human Fc receptor presenting murine fibroblasts in the "CD40 system", especially in relation to cultured plasma cells. Finally, some important applications of the "CD40 system" are also summarized. (63 Refs.)
Record Date Created: 19970116

9/7/15 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

125027647 CA: 125(3)27647c PATENT
Genetic therapy of diseases caused by the immune system using a genetic construct regulated in a cell- or virus-specific, cell cycle-dependent manner
INVENTOR(AUTHOR): Sedlacek, Hans-Harald; Mueller, Rolf
LOCATION: Germany,
ASSIGNEE: Behringwerke Ag
PATENT: PCT International ; WO 9606941 A1 DATE: 960307
APPLICATION: WO 95EP3371 (950825) *GB 9417366 (940826) *GB 956466 (950329) *DE 19524720 (950712)
PAGES: 111 pp. CODEN: PIXXD2 LANGUAGE: German CLASS: C12N-015/85A; A61K-048/00B DESIGNATED COUNTRIES: AM; AU; BB; BG; BR; BY; CA; CN; CZ; EE; FI; GE; HU; JP; KG; KP; KR; KZ; LK; LR; LT; LV; MD; MG; MN; MX; NO; NZ; PL; RO; RU; SI; SK; TJ; TT; UA; US; UZ; VN DESIGNATED REGIONAL: KE; MW; SD; SZ ; UG; AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; NE; SN; TD; TG
SECTION:
CA203001 Biochemical Genetics
CA215XXX Immunochemistry
IDENTIFIERS: gene therapy immune system disease, cdc25C gene promoter CDE CHR element, cell cycle dependent regulation gene therapy
DESCRIPTORS:
Gene,animal...
cdc25C, CDE and CHR elements of; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner
Genetic element...
CDE (cell cycle-dependent element); genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner
Gene,animal, cdc2...
CDE and CHR elements of; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner
Antigens...
CD40L, gene for; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner
Leukemia...
cell; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner
Genetic element,promoter...

cell-cycle dependent; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

Genetic element...
CHR (cell cycle genes homol. region); genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

Proteins,specific or class,biological studies...
cytotoxic, gene for; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

Immunity...
diseases caused by; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

Genetic element...
E box of myc gene; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

Gene,animal...
E2A-PBX-1, transcription regulatory element of; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

Animal growth regulators,blood platelet-derived growth factors... Retinoids ... Transferrins...
for targeting; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

Proteins,specific or class,biological studies...
GADD45, gene for; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

Proteins,specific or class,biological studies...
gene bak, gene for; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

Bacteria... Borrelia burgdorferi... Campylobacter pyloridis... Malaria... Virus,animal, hepatitis A... Virus,animal, hepatitis D... Virus,animal, hepatitis E... Virus,animal, herpes... Virus,animal, influenza... Virus,animal, measles... Virus,animal, parainfluenza V... Virus,animal, rabies... Virus,animal, rota-... Virus,animal, Rous sarcoma...
Virus,animal, varicella-zoster...
gene for antigens of; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

Phosphoproteins,cyclins A...
gene for, CDE and CHR elements of; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

Enzymes...
gene for cytostatic precursor-cleaving; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

Antibodies...
gene for immunosuppressive; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

Cell cycle...
gene for inhibitors of; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

Animal growth regulators... Animal growth regulators,.beta.-transforming growth factors... Antigens,CD28... Antigens,CD2... Antigens,CD3... Antigens,CD40... Antigens,CD4... Antigens,CD8... Interferons,.alpha.... Interferons,.beta.... Lymphokines and Cytokines,interleukins... Lymphokines and Cytokines,perforin... Phosphoproteins,tumor suppressor, p53...

Proteins,specific or class, p130... Proteins,specific or class, P16... Proteins,specific or class, p21,biological studies... Ribonucleic acid formation factors,gene Rb... Toxins,cholera...
gene for; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner
Allergy inhibitors... Anti-infective agents... Autoimmune disease... Hematopoietic precursor cell... Inflammation inhibitors,antiarthritics... Lymphocyte... Macrophage... Neoplasm inhibitors,leukemia... Parasite... Synovial membrane,synoviocyte... Therapeutics,geno-... Virucides and Virustats...
genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner
Gene,animal...
HOX-11, transcription regulatory element of; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner
Transplant and Transplantation,host-vs.-graft reaction...
prevention of; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner
Proteins,specific or class,biological studies...
p107, gene for; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner
Antibodies,monoclonal...
targeting; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner
Receptors...
transcription regulatory element of gene for macrophage scavenger; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependen
Receptors,retinoic acid...
transcription regulatory element of gene for promyelocytic leukemia; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-depend
Hemopoietin receptors,hematopoietic cell growth factor KL... Hemopoietins,hematopoietic cell growth factors KL... Integrins,antigens LFA-1... Integrins,antigens Mac-1 (macrophage 1)... Integrins,antigens p150,95... Interferons,.gamma.... Lymphokine and cytokine receptors... Lymphokine and cytokine receptors,interleukin 1... Lymphokine and cytokine receptors,interleukin 2... Lymphokine and cytokine receptors,interleukin 3 ... Lymphokine and cytokine receptors,interleukin 4... Lymphokine and cytokine receptors,interleukin 6... Lymphokine and cytokine receptors,leukemia-inhibiting factor... Lymphokines and Cytokines... Lymphokines and Cytokines,interleukin 1.alpha.... Lymphokines and Cytokines,interleukin 1.beta.... Lymphokines and Cytokines,interleukin 10 ... Lymphokines and Cytokines,interleukin 11... Lymphokines and Cytokines,interleukin 12... Lymphokines and Cytokines,interleukin 13... Lymphokines and Cytokines,interleukin 3... Lymphokines and Cytokines,interleukin 4... Lymphokines and Cytokines,interleukin 5... Lymphokines and Cytokines,interleukin 6... Lymphokines and Cytokines,interleukin 7... Lymphokines and Cytokines,interleukin 8... Lymphokines and Cytokines,interleukin 9... Lymphokines and Cytokines,leukemia-inhibiting factor... Lymphokines and Cytokines,tumor necrosis factor-.alpha.... Lymphokines and Cytokines,tumor necrosis factor-.beta.... Receptors,colony-stimulating factor 1... Receptors,colony-stimulating factor 2... Receptors,cytokine... Receptors,hematopoietic cell growth factor KL... Receptors,interleukin 1... Receptors,interleukin 2... Receptors,interleukin 3... Receptors,interleukin 4... Receptors,interleukin 6... Receptors,leukemia-inhibiting factor... Ribonucleic acid formation factors,ISGF-2 (interferon-stimulated gene factor 2)...
transcription regulatory element of gene for; genetic therapy of

diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner
Gene,animal, bcl-1... Gene,animal, bcl-2... Gene,animal, bcr-c-abl... Gene,animal, c-myc... Virus,animal... Virus,animal, cytomegalo-... Virus,animal, Epstein-Barr... Virus,animal, hepatitis B... Virus,animal, hepatitis C... Virus,animal, herpes simplex 1... Virus,animal, herpes simplex 2... Virus,animal, human immunodeficiency... Virus,animal, human immunodeficiency 1... Virus,animal, human immunodeficiency 2... Virus,animal, human immunodeficiency 3... Virus,animal, human papilloma... Virus,animal, human papilloma 16... Virus,animal, human papilloma 18... Virus,animal, human T-cell leukemia... Virus,animal, simian 40...
transcription regulatory element of; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner
Animal cell...
virus-infected; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

CAS REGISTRY NUMBERS:

9004-10-8 biological studies, for targeting; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

59-23-4 biological studies, ligand contg., for targeting; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

177792-80-2 CDE element of cdc25C gene; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

177323-66-9 CDE-CHR element-contg. cdc25C fragment; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

177792-83-5 CHR element of cdc25C gene; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

61912-98-9 62031-54-3 62229-50-9 for targeting; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

9002-06-6 gene for herpes simplex virus; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

150428-23-2 gene for inhibitor of; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

9001-45-0 9001-92-7 9003-99-0 9013-05-2 9013-79-0 9014-42-0 9025-05-2 9031-98-5 9032-92-2 9035-73-8 9037-41-6 9054-89-1 9073-60-3 9075-21-2 9075-38-1 11096-26-7 37205-61-1 57534-78-8 106178-18-1 106956-32-5 gene for; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

3458-28-4 ligand contg., for targeting; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

177835-73-3 177835-74-4 nucleotide sequence; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

9001-12-1 79955-99-0 83869-56-1 86102-31-0 124861-55-8 140208-24-8 141907-41-7 143011-72-7 145809-21-8 146480-35-5 146480-36-6 transcription regulatory element of gene for; genetic therapy of diseases caused by immune system using genetic construct regulated in cell- or virus-specific, cell cycle-dependent manner

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ds

Set     Items   Description
S1        367   (CD40L OR CD40(W)LIGAND) AND LEUKEMIA?
S2        128   S1 AND (TREAT? OR THERAP?)
S3         86   RD S2 (unique items)
S4         89   S1 AND (INHIBIT? OR SUPPRESS? OR TREAT? OR THERAP? OR ANTA-
              GONI?)(20N)(LEUKEMIA?)
S5         65   RD S4 (unique items)
S6         14   S1 AND REVIEW?
S7         11   RD S6 (unique items)
S8         22   S1 AND PY=1996
S9         15   RD S8 (unique items)
? s s1 and py=1995

            367  S1
        1957661  PY=1995
    S10      20  S1 AND PY=1995
? rd s10

...completed examining records
    S11      10  RD S10 (unique items)
? t s11/7/all


 11/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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10180214   BIOSIS NO.: 199698635132
Study of CD40 ligand expression in B-cell chronic lymphocytic
  leukemia.
AUTHOR: Brugnoni Duilio; Rossi Giuseppe; Tucci Alessandra; Cattaneo Roberto
  ; Airo Paolo(a)
AUTHOR ADDRESS: (a)Servizio di Immunol. Clinica, Spedali Civili, Piazzale
  Spedali Civili 1, 25123 Brescia**Italy
JOURNAL: Haematologica  80 (5):p440-442 1995
ISSN: 0390-6078
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: CD40 ligand (CD40L) is a membrane molecule that
  plays a key role in T cell-B cell cooperation, providing B cells the
  helper signals needed for activation, proliferation, differentiation and
  prevention of apoptosis. Patients with B-cell chronic lymphocytic
  leukemia (B-CLL) were studied to verify the following hypotheses:
  a) whether defective CD40L expression on activated T cells could
  account for deficient helper signals and therefore for
  hypogammaglobulinemia; b) whether aberrant CD40L expression on B
  cells could be a mechanism by which leukemic cells stimulate themselves
  via CD40 to escape apoptosis. Results showed physiological expression of
  CD40L on in vitro activated CD4+ cells, while this expression was
  absent on fresh and activated B cells. Abnormalities in CD40/CD40L
  interaction do not seem to play a role either in the pathogenesis of
  hypogammaglobulinemia or in lymphocyte accumulation in B-CLL.


 11/7/2     (Item 2 from file: 5)
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DIALOG(R)File 5:Biosis Previews(R)

10180161 BIOSIS NO.: 199698635079
The expression of CD26 and **CD40 ligand** is mutually exclusive in human T-cell non-Hodgkin's lymphomas/**leukemias**.
AUTHOR: Carbone Antonino(a); Gloghini Annunizata; Zagonel Vittorina; Aldinucci Donatella; Gattei Valter; Degan Massimo; Improta Salvatore; Sorio Roberto; Monfardini Silvio; Pinto Antonio
AUTHOR ADDRESS: (a)Div. Pathol., Centro Regionale Riferimento Oncologico, IRCCS, via Pedemontana Occidentale, Avian**Italy
JOURNAL: Blood 86 (12):p4617-4626 **1995**
ISSN: 0006-4971
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: CD26 and **CD40 ligand** (**CD40L**) are surface molecules on human activated T lymphocytes that play a critical role in the regulation of lymphopoiesis. Both molecules are expressed on a restricted fraction of human T-cell non-Hodgkin's lymphomas (NHL)/**leukemias**; however, little is known about their functional and/or clinical significance in these disorders. In this study, the pattern of expression of **CD40L** was compared with that of the CD26 molecule. A series of 67 human T-cell NHL/**leukemias** and a panel of **leukemia**/lymphoma T-cell lines were evaluated by immunohistochemistry, flow cytometry, and RNA studies. The overall frequency of CD26+ and **CD40L**+ samples was rather similar (25/67 (37%) v 18/67 (27%)). However, the majority of CD26-expressing cases clustered in the lymphoblastic lymphomas (LBL)/T-acute lymphoblastic **leukemias** (ALL; 12/23) and CD30+ anaplastic large-cell (ALC) lymphomas (5/8), whereas **CD40L**+ lymphomas included a large fraction of mycosis fungoides (11/21 (52%)). CD26 and **CD40L** coexpression was found only in 2 mycosis fungoides cases and 1 small lymphocytic lymphoma, Thus, the expression of the two antigens was mutually exclusive in almost all T-cell lymphomas/**leukemias**. Accordingly, lymphoma cell lines expressed either one of the molecules or the relative amounts of CD26 and **CD40L** were inversely proportional. In contrast, reactive T lymphocytes from patients with non-neoplastic T-cell expansions and in vitro activated CD3+ or CD4+ normal T cells were found to coexpress **CD40L** and CD26. Results of a multivariate analysis showed that the expression of CD26 in T-cell LBL/ALL patients was associated to a worse outcome in terms of survival, as compared with patients with CD26-tumors (P ltoreq .0001). Based on our results, it can be concluded that, (1) as opposed to activated or reactive normal T cells, the expression of CD26 and of **CD40L** is mutually exclusive in human T-cell lymphomas/**leukemias**; (2) expression of CD26 is restricted to aggressive pathologic entities, such as T-cell LBL/ALL and T-cell CD30+ ALC lymphomas, whereas **CD40L** is expressed on slow progressing diseases such as mycosis fungoides; and (3) within the T-cell LBL/ALL group of tumors, CD26 may identify a subset of poor prognosis patients.

11/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10167305 BIOSIS NO.: 199698622223
Expression and function of CD95 (APO-1/FAS) antigen on B-cell malignancies stimulated by **CD40 ligand** and IL-4.
AUTHOR: Wang Dakun; Ritz Jerome; Robertson Michael J
AUTHOR ADDRESS: Div. Hematol. Malignancies, Dana Farber Cancer Inst., Boston, MA**USA
JOURNAL: Blood 86 (10 SUPPL. 1):p602A **1995**
CONFERENCE/MEETING: 37th Annual Meeting of the American Society of Hematology Seattle, Washington, USA December 1-5, 1995

ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

11/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10165138 BIOSIS NO.: 199698620056
Growth inhibition of human multiple myeloma cells by the **CD40 ligand** GP39.
AUTHOR: Tong A W; Seamour B K; Ordonez G; Stone Marvin J
AUTHOR ADDRESS: Charles Sammons Cancer Cent., Baylor Univ. Med. Cent., Dallas, TX 75246**USA
JOURNAL: Blood 86 (10 SUPPL. 1):p59A **1995**
CONFERENCE/MEETING: 37th Annual Meeting of the American Society of Hematology Seattle, Washington, USA December 1-5, 1995
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

11/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10064605 BIOSIS NO.: 199598519523
CD40 ligand is constitutively expressed in a subset of T cell lymphomas and on the microenvironmental reactive T cells of follicular lymphomas and Hodgkin's disease.
AUTHOR: Carbone Antonino(a); Gloghini Annunziata; Gruss Hans-Jurgen; Pinto Antonio
AUTHOR ADDRESS: (a)Div. Pathol., Centro Regionale Riferimento Oncol., IRCCS, via Pedemontana Occidentale, Aviano I-**Italy
JOURNAL: American Journal of Pathology 147 (4):p912-922 **1995**
ISSN: 0002-9440
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Although CD40 has been extensively studied in Band T-cell non-Hodgkin's lymphomas (NHLs)/**leukemias**, and more recently in Hodgkin's disease (HD), little is known about the expression of its ligand (**CD40L**) in lymphoproliferative disorders other than T-cell NHLs/**leukemias**. A series of 121 lymphoma/**leukemia** samples, including 35 cases of HD, 34 T-cell and 39 B-cell NHLs, 2 cases of adult T-cell **leukemia**/lymphoma, and 11 cases of T-cell acute lymphoblastic **leukemia**, were evaluated for **CD40L** expression by immunostaining of frozen tissue sections and flow cytometry with the anti-**CD40L** monoclonal antibody M90. **CD40L** was constitutively expressed by neoplastic cells in 15 of 36 (42%) T-cell NHLs/adult T-cell **leukemia**/lymphomas, almost invariably those displaying the CD4+/CD8-phenotype, whereas no **CD40L**-expressing tumor cells could be found in B-cell NHL and HD. Among T-cell acute lymphoblastic **leukemias**, **CD40L** was detected only on 2 cases displaying a stem-cell-like phenotype. In follicular B-cell lymphomas a large number of **CD40L**-expressing CD3+/CD4+ T lymphocytes were found admixed with tumor cells within the neoplastic follicles and in their surrounding areas. In the nonfollicular B-cell lymphomas, **CD40L**-positive CD3+/CD4+ T lymphocytes were few or absent. In all HD subtypes other than the nodular lymphocytic predominance, **CD40L**-expressing CD3+/CD4+ T lymphocytes were numerous in the HD-involved areas and were mainly located in close proximity to the Reed-Sternberg cells. Our data indicate that in human lymphomas **CD40L** is preferentially expressed by a restricted subset of T-cell lymphomas, mostly with CD4 immunophenotype.

Finally, we have provided morphological evidence that **CD40L** may play an important role in the cell contact-dependent interaction of tumor B-cells (CD40+) within the neoplastic follicles or Reed-Sternberg cells (CD40+) in HD-involved areas and the microenvironmental CD3+/CD4+/ **CD40L**+ T lymphocytes.

11/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09782593 BIOSIS NO.: 199598237511
CD40 Ligand triggered interleukin-6 secretion in multiple myeloma.
AUTHOR: Urashima Mitsuyoshi; Chauhan Dharminder; Uchiyama Hiroshi; Freeman Gordon J; Anderson Kenneth C
AUTHOR ADDRESS: Div. Hematologic Malignancies, Dana-Farber Cancer Inst., Boston, MA 02115**USA
JOURNAL: Blood 85 (7):p1903-1912 **1995**
ISSN: 0006-4971
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Previous studies have suggested that interleukin-6 (IL-6) may mediate growth of multiple myeloma (MM) in either an autocrine or paracrine growth mechanism. However, those molecules which can trigger IL-6 secretion either by tumor cells or non-MM marrow cells are not well characterized. In the present study, we have examined the expression and functional significance of CD40 on MM and plasma cell **leukemia** (PCL) cells and derived cell lines, as well as long-term bone marrow stromal cells (BMSCs) and derived cell lines. CD40 was expressed on the majority of MM cells (gt 90%) and BMSCs (gt 70%). Triggering via CD40 using NIH3T3 **CD40 ligand** transfectant (CD40LT) cells increased (gt 30%) cell surface CD80, CD18, CD11a, CD11b, and CD11c expression on MM cell lines. Culture with either fresh or paraformaldehyde fixed NIH3T3 CD40LT cells upregulates IL-6 secretion in MM cells and MM-derived cell lines, as well as normal and MM bone marrow mononuclear cells (BMMCs), BMSCs, and BMSC lines; this effect can be specifically blocked by anti-CD40 monoclonal antibody (MoAb). BMMCs and BMSCs from patients with MM secreted significantly more IL-6 than those from healthy donors (n = 3, P lt .001); moreover, after stimulation using **CD40L**, IL-6 secretion was fourfold greater (n = 3, P lt .001) from MM BMMCs and BMSCs than from normal BMMCs and BMSCs. Myeloma (CD38+CD45RA-) cells and non-MM (CD38+CD45RA+, CD38-CD45RA+, and CD38-CD45RA-) BMMCs were separated by dual fluorescence cell sorting. The latter secreted fourfold more IL-6 than the former (n = 2, P lt .001). Increased IL-6 secretion (up to 28-fold) and proliferation (Stimulation Index 10) by CD38+CD45RA-MM cells was triggered by culture with NIH3T3 CD40LT cells. Finally, anti-CD40 MoAb partially (30%) blocked tumor cell to BMSC adhesion-induced IL-6 secretion. These studies support the view that **CD40L** may trigger IL6 secretion by both MM cells and BMSCs and that IL-6-mediated autocrine and paracrine growth mechanisms may be possible in MM.

11/7/7 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

06294863 EMBASE No: 1995330649
CD40 ligation induces Apo-1/Fas expression on human B lymphocytes and facilitates apoptosis through the Apo-1/Fas pathway
Schattner E.J.; Elkon K.B.; Yoo D.-H.; Tumang J.; Krammer P.H.; Crow M.K.; Friedman S.M.
Hospital for Special Surgery, 535 East 70th Street,New York, NY 10021

United States
Journal of Experimental Medicine (J. EXP. MED.) (United States) 1995, 182/5 (1557-1565)
CODEN: JEMEA ISSN: 0022-1007
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The Apo-1/Fas antigen (CD95) mediates programmed cell death of lymphocytes when bound by Fas ligand or anti-Apo-1/Fas antibody. In contrast, the CD40 antigen provides a potent activation and survival signal to B lymphocytes when it is engaged by its T cell ligand (**CD40L**, gp39) or cross-linked by anti-CD40 antibody. In this study, we use human tonsillar B cells and the Ramos Burkitt's lymphoma B cell line, which serves as a model for human germinal center B lymphocytes, to study the effectors of Apo-1/Fas expression and apoptosis of human B cells. We found that Apo-1/Fas expression was upregulated on both malignant and normal human B lymphocytes after CD40 ligation induced by (d) cognate T helper-B cell interaction mediated by microbial superantigen (SAg); (b) contact-dependent interaction with CD40Lsup +, but not CD40Lsup + Jurkat mutant T cell clones; and (c) monoclonal anti-CD40, but not any of a panel of control antibodies. Enhanced B cell Fas/Apo-1 expression is functionally significant. Coculture of Ramos Burkitt's lymphoma line cells with irradiated SAg-reactive CD4sup + T-cells with SAg or CD40Lsup + Jurkat T cells results in B cell apoptosis, evidenced by reduced cell viability and DNA laddering. This process is augmented by the addition of anti-Apo-1/Fas monoclonal antibody, consistent with an acquired susceptibility to Apo-1/Fas-mediated apoptosis. These data support an immunoregulatory pathway in which seemingly contradictory signals involving the B cell proliferation/survival antigen CD40, as well as the Apo-1/Fas molecule, which mediates programmed cell death of lymphocytes, are linked in the process of human B cell activation.

11/7/8 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

06254786 EMBASE No: 1995290807
Induction of CD40 in promyelocytic HL60 cells cultured with retinoic acid and/or various cytokines
Shinagawa T.; Nunoi H.; Nonoyama S.; Kanegasaki S.
The Institute of Medical Science, The University of Tokyo, 4-6-1 Shirokanedai,Minato-ku, Tokyo 108 Japan
Journal of Biochemistry (J. BIOCHEM.) (Japan) 1995, 118/3 (534-540)
CODEN: JOBIA ISSN: 0021-924X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The antigenic protein CD40 on the surface of B lymphocytes plays an important role in their proliferation, immunoglobulin class switching, and rescue from apoptosis in the germinal center through interaction with T lymphocytes expressing **CD40 ligand**, The protein is also found on the cell surface of other antigen-presenting cells such as monocytes, dendritic cells, and thymic epithelium cells, but its presence in other myeloid cells has not been reported. We show here that CD40 protein is induced in promyelocytic HL60 cells, when cultured with retinoic acid, a vitamin that converts them to granulocyte-like cells. The cultured cells also expressed CD15, a marker for granulocytes, and cytochrome b$D5$D5inf 8, an essential component of the superoxide-generating system in phagocytes, on their surface, No detectable amount of mRNA for CD40 was found in naive HL60 cells, whereas a large amount of the message was induced in the cells cultured with the vitamin. Although CD40 expression was enhanced when the cells were further cultured with GM-CSF or IFN-gamma, expression of CD14, a marker for monocytes, was also enhanced. HL60 cells, therefore, express CD40 protein during differentiation not only toward monocytes but also toward granulocytes, at least transiently.

11/7/9 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

06073563 EMBASE No: 1995104040
Tumor necrosis factor-alpha facilitates induction of CD80 (B7-1) and CD54 on human B cells by activated T cells: Complex regulation by IL-4, IL-10, and **CD40L**

Ranheim E.A.; Kipps T.J.
Department of Medicine, University of California, San Diego, 9500 Gilman Drive,La Jolla, CA 92093-0663 United States

Cellular Immunology (CELL. IMMUNOL.) (United States) 1995, 161/2 (226-235)
CODEN: CLIMB ISSN: 0008-8749
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Expression of immune accessory molecules, such as CD80 (B7-1), on antigen-presenting cells governs whether such cells can activate antigen-specific T cells. As such, the factors that regulate the expression of these accessory molecules may determine whether presentation of antigen leads to immune activation or anergy. We previously reported that anti-CD3-activated T cells (T(a)) can induce expression of CD80 and CD54 (ICAM-1) on human B cells through a contact-dependent signal delivered to the CD40 molecule via the **CD40 ligand**. Here, we demonstrate that another molecule in the **CD40-ligand** family, namely tumor necrosis factor-alpha (TNF-alpha), also plays a role in the T(a)-mediated induction of CD80 or CD54 on human B cells. Neutralizing mAbs specific for TNF-alpha can inhibit B cell expression of CD80 or CD54 that is induced when B cells are cultured with T(a) cells or in T(a)-cell conditioned media. Moreover, soluble, recombinant TNF-alpha or TNF-beta can induce significant increases in B cell expression of CD80 and CD54. The phenotypic changes effected by TNF-alpha can be recapitulated by crosslinking CD120b (p75 TNF-receptor), but not CD120a (p55 TNF-receptor), with mAbs presented on FcgammaRII (CD32)-expressing L cells. IL-4 augments the expression of CD80 induced by crosslinking either CD40 or CD120b. However, although IL-10 augments CD40-induced expression of CD80, this cytokine inhibits the expression of CD80 that is induced by crosslinking CD120b. Further regulation of TNF-mediated CD80 expression may occur at the level of CD120b expression itself. We find that stimulation with exogenous IL-4 or CD40-crosslinking induces B cell expression of CD120b, but not CD120a. This study identifies an ancillary, TNF-mediated pathway, whereby activated T cells can induce B cells to express enhanced levels of the important co-stimulatory molecules, CD80 and CD54.

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Transfection of the c-myc oncogene into normal Epstein-Barr virus-harboring B cells results in new phenotypic and functional features resembling those of Burkitt lymphoma cells and normal centroblasts

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Activated c-myc gene was introduced into the cells of three normal

Epstein-Barr virus (EBV)-positive lymphoblastoid B cell lines (LCL). The cells were monitored for the appearance of new phenotypic and functional features compared with the control LCL cells transfected with plasmid that did not contain the c-myc gene. The LCL-expressing c-myc constitutively did not arrest growth in low serum concentration. However, the cell number in the cultures failed to increase because of substantial cell death. Death was due to apoptosis as demonstrated by flow cytometric analysis of propidium iodide- stained cells, by typical DNA laddering in gel electrophoresis, and by the inspection of Giemsa-stained cell smears. Apoptosis was also induced by exposing the transfected cells to antibodies directed to the immunoglobulin mu chain (a-mu-ab) irrespective of the serum concentration in the culture. Exposure of the cells to **CD40 ligand** (**CD40L**) or CD40 monoclonal antibody prevented cell apoptosis. Upon transfection with c-myc, the LCL cells acquired a vacuolated morphology that was never observed in control cells. Moreover, the expression of CD10 and CD38 was upregulated, while that of CD39 and especially CD23 was downregulated. Unlike that observed in certain Burkitt lymphoma (BL) cell lines that share the same surface phenotype (CD10sup +CD38sup +CD23sup -CD39sup -), the c-myc-transfected cells expressed lymphocyte function-associated (LFA) 1, LFA-3, and intercellular adhesion molecule 1 and grew in large clumps rather than single-cell layers. Expression of CD10 and CD38 was particularly evident on the cells undergoing apoptosis, thus suggesting a correlation between the presence of these markers and the apoptotic process. Cells placed in conditions favoring in vitro apoptosis displayed downregulation of Bcl-2 protein. Bcl-2 expression was, however, upregulated when the cells were exposed to **CD40L**. These data indicate that the B cells expressing c-myc constitutively acquire some of the features of normal centroblasts and of BL cells, including the expression of CD10 and CD38, and the propensity to undergo apoptosis, which can be prevented by exposure to **CD40L**. Therefore, these cells can serve as a model system to study both BL lymphomagenesis as well as the process of B cell selection occurring in the germinal centers.